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IMMUNOLOGIC STUDIES OF POLLINOSIS

VI. SHORTENING THE TREATMENT OF HAY FEVER

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THE experiments to be described are the outgrowth of six years of investigation into the relationship between clinical hay fever and the so-called blocking, or thermostable, antibody. Before reporting our findings, brief reference will be made to those who discovered the antibody, first in the blood stream and later in the tissues of treated allergic patients. Mention will be made of investigations which revealed that this immune factor resembles conventional antibodies insofar as the phenomenon of recall is concerned. Observations lending weight to the theory that the antibody plays a protective role in man will be reported.

New data will then be presented to show that satisfactory immunity can be built up by the use of short "booster" courses of pollen extract, and that the customary, prolonged treatment advocated by many allergists as a preseasonal stimulus for their hay fever cases may be unnecessary after the first year of therapy.

HISTORICAL REVIEW

Shortly after the demonstration of the skin-sensitizing capacity of allergic serum by Prausnitz and Küstner[1] in 1921, the existence of more than one type of antibody against allergens was suggested in the European literature. Van Leeuwen and Kremer[2] noted that serum containing Prausnitz-Küstner (PK) antibodies for molds tended to reduce the response of mold-sensitive skin to this antigen. The following year Jadassohn[3] described this neutralizing tendency for ascaris-sensitive serum which he tested along with ascaris extract in appropriate passive transfer sites. It is interesting that both van Leeuwen and Jadassohn concluded that the sensitizing and neutralizing functions

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were properties of one, rather than of two, antibodies in the serum. However, in 1930, Gyorgy, Moro, and Witebsky[4] claimed that the serum of egg-allergic children could be distinguished from that of egg-immune infants by means of their different zones of complement fixation; and, by 1932, Woringer[5, 6] referred to "deux sortes d'anticorps ovalbuminiques" in the blood of nurslings. The latter investigator showed that egg white failed to produce the PK antibody in infants not congenitally predisposed to allergy, but that the antigen did elicit another type of immune response in them, and that this antibody fixed complement in a characteristic zone which differed from that of the allergic variety. He gave further impetus to the theory of two antibodies when he proved that attempts to "desensitize" allergic subjects increased, rather than diminished, their allergic antibodies. This finding was in confirmation of the suggestion of Levine and Coca,[7] who had arrived at the same conclusion by the serum dilution method of passive transfer, whereas Woringer had devised a quantitative procedure for exhausting the sensitizing power of the serum with graded amounts of antigen. It became necessary to assume that some mechanism other than that of desensitization was operative in successfully treated patients.

In 1935 Cooke, Barnard, Hebald, and Stull[8] made another contribution to the hypothesis of two antibodies by observing that the serum of some pollen-sensitive individuals was altered by specific therapy. After a series of injections, there was a reduction in the amount of whealing which occurred when the patient's serum was mixed with pollen antigen and tested in normal skin. To explain this they postulated the development during therapy of an immune body which differed from reagin. Because this interference with whealing was noted in serum-antigen mixtures tested in normal skin but could not be demonstrated by similar tests performed in naturally sensitive skin, they referred to the hypothetical factor as a "peculiar, blocking or inhibiting type of immune antibody." Harley[9] concurred in their belief that the immune body did not bind its antigen. Later[10] it became apparent that the failure of the antibody to bind its antigen rested upon the use, by these workers, of excessive proportions of antigen.

Within the next two years, Cooke, Loveless and Stull[11] succeeded in producing pollen-immune serum in normal volunteers. At the end of a course of pollen injections, the sera of the three subjects possessed the "blocking" faculty but lacked all capacity to sensitize normal skin for the pollen antigen. At the same time, Cohen and Nelson[12] were independently developing the same type of immune factor in sheep by means of pollen injections. It was natural to assume that such an antibody existed in treated hay fever patients but it was not until two years later[10] that a technique was evolved for demonstrating its existence in allergic serum. It was possible to destroy the activity of the reagin by means of controlled heating and then to measure the antigen-neutralizing power of the serum. Concurrent studies of these heated sera from

treated patients and of the sera of pollen-inoculated, normal subjects established the existence of the same antibody in the two groups. This induced antibody was found regularly to bind and inactivate its pollen antigen, as demonstrated by negative reactions in both naturally and artificially sensitized skin when serum-antigen mixtures were used for tests. The neutralizing capacity was definite but limited, urticarial responses being detected when excessive amounts of antigen were used in the mixtures. The antibody differed from reagin not only in its capacity to withstand heat and in its failure to sensitize skin but also in the speed with which it disappeared from inoculated cutaneous sites. Furthermore, when mixed in vitro with reagin it appeared to possess a greater affinity for the common antigen than reagin, so that no whealing occurred in an injected cutaneous site until antigen *in excess* of the needs of the thermostable antibody had been included in the test mixture. This observation led very naturally to the theory that the antibody might exert a protective influence upon its allergic possessor.

However, it was not to be expected that protection would be afforded by antibody in the blood stream inasmuch as the portal of entry for atmospheric pollen is the allergic tissues of the eye, nose, and bronchi. By means of delicate tests, calling for small amounts of antigen which revealed the threshold of response in the skin and in the conjunctiva, it was learned that neutralizing antibody was also acquired by the *tissues* during therapy.[13]. As the concentration of thermostable antibody rose and fell in the circulation, the tolerance of the tissues for antigen rose and fell with it.

The protective power of the thermostable antibody was further tested by means of transfusion. When patients acutely ill with hay fever were transfused with several hundred cubic centimeters of blood or serum which had been taken from pollen-inoculated normal subjects, temporary amelioration of their symptoms resulted.[14] This beneficial effect stood in contrast to other transfusion experiments[15] performed with reaginic blood taken from proved, untreated cases of ragweed hay fever. The nonallergic recipients developed marked nasal, conjunctival, and cutaneous allergy to the related antigen.

Although the above observations pointed clearly to the existence of an antigen-inactivating body in the blood and tissues of pollen-inoculated patients, the effective role of the antibody was still far from clear. One reason for this was that no regular correlation appeared to exist[13, 16] between the blood antibody and the extent of clinical improvement in series of individuals. Although the incidence of satisfactory results in a group for a given year was greater among patients with high titers than among those with low titers, there were exceptions.

This situation did not, however, rule out the hypothesis that the antibody plays a protective role in hay fever, because important variables were present in the test. The patient's appraisal of improvement, for example, varied decidedly from individual to individual. Still more

important was the variable introduced by the *test subject* into the titration end point obtained for the serum in passive transfer experiments. So definite was this factor that only those titers determined in the same test subject could legitimately be used for comparison. This meant that, at most, ten serum specimens could be compared with one another. Even after this requirement had been met, it was found that still another variable had to be dealt with; viz., one individual appeared to need more antibody than another for a given degree of clinical refractoriness. Although the titer required for the protection of one individual did not differ by more than threefold from that required by another, this variable could not be disregarded. These three factors were not mentioned by Cooke when he expressed doubt as to the protective nature of thermostable antibody.[16]

In order to minimize these variables, a "longitudinal" study of individual patients over a number of years was carried out by the author,[17] comparisons being limited to the different sera of one patient which could be titrated simultaneously. Utilizing this individual approach for fifty-two patients who had been observed for from three to five years, a correlation was regularly found between thermostable antibody and the clinical refractoriness of the given patient to atmospheric pollen. When the seasonal antibody titer was above a certain level (which varied somewhat with the patient), the individual remained relatively free from symptoms, whereas his complaints returned during seasons when his antibody production was low, whether or not he had received current therapy.

These observations strengthened the theory that clinical resistance in hay fever may depend, at least partially, on neutralizing antibody. The next step was an inquiry into the best ways of producing the thermostable factor. Earlier experiments with normal subjects[18] had revealed that the so-called accelerated and enhanced immune response (familiar to immunologists in other fields[19, 20]) could be elicited by pollen injections once the recipient had experienced a primary course and had been allowed to go without treatments for three to six months before being given his "booster" series. When this principle was cautiously applied to ragweed-sensitive patients, the same phenomenon appeared.[21] A chosen total dose could be administered in fewer injections and in less time during secondary than during primary courses, and, almost invariably, the rate of antibody formation was relatively heightened.

In view of these findings, it was logical to try to substitute immunologic principles for empiricism in the preventive management of hay fever. In 1942, with this in mind, we restricted secondary dosage to the estimated minimal needs of the individual and found that small amounts of antigen brought most patients their best clinical and serologic results. In the present experiment, we have attempted to work out a more uniform schedule which would serve our average patient as a satisfactory "booster" course. It was based on the observed im-

munologic needs and tolerances of the various members of the group and was accompanied by serologic, intracutaneous, ophthalmic, and clinical studies on each subject.

MATERIAL AND METHODS

Selection of Patients.—Forty-three patients returned for secondary therapy in 1943. Ten of them had taken their first courses the year before at The New York Hospital allergy clinic. The remainder had been under our care for from two to five years. None had ever been treated elsewhere. They had been selected solely on the basis of their clinical histories, which were unequivocally that of ragweed pollen sensitiveness. They were all found to be reactive to intracutaneous, conjunctival, and serologic tests with ragweed extract. They covered the entire range of sensitiveness from exquisitively reactive to relatively insensitive. There were not less than five cases each of the Cooke[22] skin test Types AA, A, B, C, and D among the group.

It seemed possible that during a number of years our group might have become automatically selected by the failure of dissatisfied members to return. Investigating this possibility, we found that the immunologic character of our group had not been altered for 1943 by the loss of twenty-four of its earlier members, inasmuch as the same incidence of good results had existed among those who left as among those who were to return. Most of the failures to return were traced to removal from the district, largely because of the Selective Service Act. Our 1943 group was, at any rate, representative of ragweed-sensitive adults of various ages and of both sexes living in the New York area.

Immunologic Classification of Cases.—Inasmuch as all patients had been followed immunologically throughout their entire period of specific treatment, we know for each roughly how much antibody he was producing when he was exhibiting his best clinical resistance. Once this protective antibody titer had been established by means of passive transfer studies such as have been previously described,[10, 13] it was relatively simple to learn approximately how little antigen would give rise to this desired concentration of immune body in a subsequent course. The smallest total dose capable of producing the protective titer in a secondary course was then noted as the "minimal protective dose" for that patient. All that remained was to put this booster dose to the clinical test of a season. If the estimated protective dose was followed by excellent clinical immunity, with 90 to 100 per cent of the original hay fever eliminated, the protective dose (PD) was assumed to have been *confirmed*. If the associated hay fever represented a good result, with 75 to 85 per cent of symptoms obviated, and this represented the patient's best response to date, we termed the total dose a *tentative PD*. If the PD had been ascertained but had not yet been put to the test of a season, it was referred to as an *estimated PD*.

As a preliminary to treatment, the forty-three subjects who returned for care in 1943 were divided into four groups according to our im-

munologic knowledge of them. The first three groups had been immunologically graded. Group 1 consisted of sixteen members whose protective dose of 10,000 or fewer protein nitrogen (PN) units had been *confirmed* by a season of excellent resistance. Group 2 contained nine others whose PD of 10,000 units had been classed as tentative in view of an associated good result. The group also contained a tenth case for whom 41,000 units appeared to be the tentative requirement. In Group 3 were three individuals whose protective titers were known but whose minimal protective dose of 10,000 units had not been put to the test of a season. For them 10,000 units constituted an *estimated PD.*

The remaining fourteen cases fell into the category of those whose PD was as yet "undetermined." Among the members of Group 4 were nine individuals who had received their primary treatments in 1942; four others had not procured as much relief as 75 per cent so that their PD could not be judged. One young man had been on perennial treatment for several years and had not been serologically studied after small total doses.

Selection of Dose for Forty-Three Cases in 1943.—It was planned to give a course of 10,000 units to all but one of the twenty-eight immunologically assayed cases whose confirmed, tentative, or estimated PD had in the past been placed at 10,000 units or below. The exception was a woman who had reported good benefit after this dose. She was tried on 43,500 units in 1943 to see whether excellent resistance would result. Her situation was essentially reversed in a twenty-ninth individual who was known to require nearly 50,000 units ("tentative" PD, 41,000) but who was deliberately restricted to 10,000. This small total dose was also selected for ten unassayed patients, bringing the number of patients on the 10,000 unit schedule to a total of thirty-eight. The remaining four subjects with ungraded needs were arbitrarily injected with doses ranging from 20,000 to 50,000 units.

Preparation of Pollen Antigen Solutions.—Ether defatted pollens of low and of high ragweed were individually extracted in the cold in the proportion of 5 Gm. to 100 c.c. of alkaline saline solution to which merthiolate had been added to give a final concentration of 1:10,000. Within five days of the onset of extraction, the sterile extracts were converted by dilution, to a strength of 10,000 protein nitrogen units per cubic centimeter and were frozen and dried in order to preserve their antigenicity.*

For therapeutic purposes, equal strengths of low and of high pollen extracts were combined, whereas low ragweed extract alone was employed for tests to determine the immunity. One large batch of low, and another of mixed, ragweed extract were cryochem-processed on the same day. They sufficed for all the tests and treatments of 1943. Samples of the dried material were freshly dissolved every week for

*Pollens were extracted, frozen, and dried by E. R. Squibb & Co., for which we express gratitude.

tests so that each solution was closely comparable to all others used during the year. Therapeutic antigen was freshly dissolved every two to four weeks.

Dosage Schedules.—Guided by descriptions of localized and generalized reactions occurring in numerous patients given individualized courses during a five-year period, we designed the framework for a more uniform booster course in 1943. The proposed succession of dosage was as follows: at the first visit, 100 PN units were given cautiously in three or four doses at half-hour intervals. The treatment was intercepted if any generalized or undue localized reaction was noted. Thereafter, unless contraindicated by generalized or undue localized reaction, the semiweekly doses increased to 300, then to 600, 1,000, 1,750, 2,500 and, finally, 3,750 units. This 10,000-unit, secondary regime was planned to meet the needs of the average patient in the shortest time without undue risk or discomfort. Careful note was made of the localized and of any generalized response which followed each injection, so that successive doses could be modified to suit the tolerance of the individual.

Estimation of Clinical Improvement.—From time to time during the season, an estimate of progress was requested, comparisons being made between the current season and those preceding therapy. As a check on his general impression, each subject was asked to keep a daily record of his symptoms in terms of duration and of intensity (mild, bad, or severe).

Tests.—Exact amounts of freshly dissolved cryochem-antigen were introduced into the skin and conjunctival sac in graduated dilutions adequate to reveal the threshold of response in each tissue. One hanging drop from a 26 gauge needle was instilled into the right sac every five to ten minutes, until the first slight reddening of the inner canthus occurred. Testing was continued until unequivocal allergic signs were elicited in the eye, in order to confirm the threshold end point noted earlier. The usual strengths used were: 10, 25, 50, 100, 150, 200, 300, and 400 units per cubic centimeter. It was often possible to complete the test with the first two or three strengths. The sac was then irrigated freely with physiologic solution, to guard against local immunization. A few drops of 1:1,000 epinephrine solution were finally instilled to nullify the reaction.

In the case of intracutaneous tests, 0.02 c.c. were accurately introduced from a 0.25 c.c. tuberculin syringe into duplicate sites along the left arm, the right being reserved for therapy. A series of dilutions were used to locate the threshold of response in the skin and to produce negative and also definitely positive reactions in confirmation of this threshold dose. Dilutions employed for these tests ranged from .000125 unit to 5 units per cubic centimeter and included nine intervening strengths. Physiologic saline solution was also used to evaluate nonspecific reactivity in the patient.

The conjunctival and intracutaneous tests were done just before and again in two weeks after the completion of the booster course. At the same time, blood was withdrawn for serologic titration.

Serologic Titrations.—Approximately 30 c.c. of blood were taken, aseptically, before and at the conclusion of each course. The serum was separated from the cells by means of centrifugation. A portion of each serum was heated in a water bath, at 60° C., for one hour, to inactivate the reagin. The neutralizing power of the heated serum for ragweed antigen was then determined by passive transfer experiments.[10, 13] One large supply of reaginic serum, obtained from an untreated case, was used for the creation of standard sensitized sites in successive, normal, test subjects. The amount of antigen required to exhaust this uniform site in different subjects ranged from 100 to 800 PN units per cubic centimeter of serum. This figure was subtracted from the higher end points found in the presence of immune serum. The difference represented the titer of thermostable antibody for the heated, immune serum involved. This precaution was taken in the hope of minimizing the influence of the test subject on the titration end points, but did not eliminate the test-subject variable completely.

Pollen Count.—The concentration of ragweed pollen grains* in the air amounted to 1,356 per cubic yard when the daily figures for August and September were totaled. The comparable figure for 1942 was 1,641, the average for the last fifteen years being 1,756.

FINDINGS

Before presenting our results, it should be stated that six cases were eliminated from all calculations dealing with clinical results for the following reasons. One patient, whose PD of 2,000 had been "confirmed" in 1942, came in for treatment so late that her 10,000-unit course of seven coseasonal injections was not completed until the season was well past its peak. Another woman, for whom a "confirmed" PD of 2,000 units was established in 1942, reported excellent control of her hay fever during 1943. However, promptly after being informed by a dentist, early in the season of pollination, that she had an inoperable malignancy of the jaw, she developed her first attack of asthma. This continued without interruption until some weeks later when she was assured by a medical specialist that she had nothing whatsoever to worry about, whereupon the asthma abruptly ceased. Four other individuals classed as "ungraded," immunologically, have never responded with as much as 75 per cent relief regardless of whether small or large doses have been employed. One had been under specific treatment for six years, two for five years and one for two years. Three of them reported that their best result to date was obtained in 1943. It seems probable

*The pollen counts were based on slides which had been set out in the New York Meteorological Observatory of Central Park by Mr. David Morris, of the U. S. Weather Bureau, and which were analyzed by Mr. O. C. Durham.

that factors other than ragweed sensitiveness alone may be operative in some of these patients, and that others are relatively refractory to any type of specific immunization with pollen extracts. They are, at any rate, unsuitable subjects for investigations concerning the relative clinical efficacy of small and of large total doses.

TREATMENT PERIOD AND NUMBER OF CLINIC VISITS REQUIRED FOR SHORT COURSE

The average treatment period of all thirty-eight patients who were placed on the 10,000-unit regime was twenty-six days. This figure was greater than the allotted twenty-one days for two reasons: one was the failure of some patients to keep their semi-weekly appointments faithfully, and the other was the inability of certain individuals to take the course in the appointed number of injections. Some subjects, however, were able to take their series in less than seven visits. The mean number of visits was 6.8 for the entire group, and the number of injections was 7.6. (Five individuals, given 20,000 to 50,000 units, made eleven visits during an average treatment period of forty-seven days.)

Generalized Reactions During Rapid Treatment.—Any reaction remote from the site of injection, regardless of its mildness, was deemed to be a "constitutional" response. These manifestations were noted in fifteen individuals on twenty-two occasions during the 259 visits made by all members on the short regime. This means an incidence of one focal reaction in 11.8 visits. Ten of these were very slight and ten were slight in intensity, amounting to little more than a few hives, a suggestion of hay fever, erythema of the palms, etc. Two of the manifestations were of moderate severity. It was necessary to use epinephrine in only three instances.

Table I shows that nine reactions of this nature were noted in eight patients taking the course faster than prescribed, and completing their 10,000-unit total dosage in fewer than seven visits. It will be seen that three of these cases originally showed rather high conjunctival sensitivity, their threshold responses being elicited by one drop of solution containing 25 PN units per cubic centimeter. The other thirteen reactions were detected in patients taking the course in seven or more visits. Five of the seven subjects were highly reactive by eye test, belonging in Class A (10-unit threshold response) or B (25-unit threshold response).

These findings stand in contrast to those of the twenty-three individuals who took the 10,000 units without incident. Table II shows that while nine patients required the prescribed seven visits for their therapy, eight completed it in less than this time. Only two of the seventeen cases were classified as belonging to Class A by conjunctival test. On the other hand, six of the twenty-five in the group had to come more than seven times to the clinic, the additional visits being necessitated by marked localized reactions. It was interesting to find that

TABLE I

RELATION OF SPEED OF TREATMENT AND OF CONJUNCTIVAL CLASSIFICATION TO OCCURRENCE OF CONSTITUTIONAL REACTION

PATIENTS TAKING BOOSTER COURSE*	THRESHOLD OF REACTION IN CONJUNCTIVA BEFORE COURSE		NUMBER OF CLINIC VISITS	NUMBER OF GENERALIZED REACTIONS
	PROTEIN NITROGEN UNITS	CLASS		
		Less than seven visits		
Be	25	B	4	1
Fa	25	B	5	1
Kl	25	B	5	1
Ba	100	D	5	1
Ma	100	D	6	1
La	100	D	6	1
Ev	150	E	6	2
Si	150	E	4	1
		Seven visits or more		
Gr	10	A	7	3
Qu	75	D	7	3
Me N	75	D	8	1
Sch	25	B	8	1
Pe	10	A	9	1
Ar	25	B	13	2
Bau	10	A	15	2

*A total of 10,000 units in all but two cases.

TABLE II

SPEED WITH WHICH PATIENTS OF DIFFERENT CLASSIFICATIONS TOOK 10,000 UNITS WITHOUT GENERALIZED REACTION

THRESHOLD OF REACTION IN CONJUNCTIVA BEFORE COURSE		SPEED WITH WHICH COURSE COULD BE COMPLETED		
PROTEIN NITROGEN UNITS	CLASS	REGULAR* (NUMBER OF CASES)	FASTER THAN REGULAR (NUMBER OF CASES)	SLOWER THAN REGULAR (NUMBER OF CASES)
10	A	1	1	2
25	B	6	0	2
50	C	1	1	1
100	D	3	4	1
200	E	2	1	
300	F	1	1	
Unclassified		1		
Total		9	8	6

*Seven visits.

four of the six had been noted to possess high degrees of conjunctival sensitivity before the course was started.

When A and B conjunctival cases were compared with other classes, it became apparent that the incidence of generalized reaction was definitely greater among the former than among the latter. During

their intensive, 10,000-unit courses of 1943, eight of the fourteen A and B patients (57 per cent) gave constitutional responses whereas only seven of twenty-four C, D, E, and F subjects (29 per cent) did so. The incidence was about twice as great in the more sensitive individuals, therefore.

It seemed probable that two factors contributed importantly to the occurrence of generalized reactions among our group: (1) high degrees of sensitiveness as revealed by eye-test, and (2) our attempt to complete the booster course in less than the prescribed seven injections.

CLINICAL RESULTS

Immunologically Assayed Cases With a Confirmed or Estimated Protective Dose.—Of the thirty-seven suitable* patients given secondary stimuli in 1943 preseasonally, twenty-five had been immunologically classified as requiring not over 10,000 units for their optimal clinical result. In response to this booster dose in 1943, fifteen of these (60 per cent) reported excellent results, avoiding 90 per cent or more of their original complaints (Table III). Another eight developed good clinical

TABLE III

CLINICAL EFFICACY OF BOOSTER COURSE OF 10,000 UNITS OR LESS
YEAR 1943

PROTECTIVE DOSE (UNITS)	CASES	CLINICAL RESPONSE			
		EXCELLENT	GOOD	FAIR	POOR
10,000 (Confirmed)	14	9	5	0	0
10,000 (Tentative)	8	4	2	1	1
10,000 (Estimated)	3	2	1	0	0
Undetermined	8	2	5	1	0
Subtotal		17	13	2	1
Total	33	30		3	

resistance with 75 to 85 per cent of their symptoms absent. Thus twenty-three of the twenty-five assayed individuals given 10,000 units or less responded satisfactorily. The two instances of unsatisfactory results occurred, perplexingly enough, in a young man and a woman who had obtained good relief in 1942 after the small total doses of 1,000 and 6,750 units, respectively.

The patient whose PD had been *tentatively* assessed at 10,000 in 1942, but who was nevertheless given 43,500 in 1943, reported excellent relief. The larger dose will, of course, be taken as her "confirmed" PD since it produced better results than did the smaller one. Another woman, who had reported "good" benefit in 1941 following 41,000 units as a booster dose, was tried on 10,000 units in 1943. As anticipated, she developed only fair resistance, and will henceforth be given more antigen.

*Six have been discarded from the calculations related to clinical result because of extraneous factors or apparent refractoriness to specific therapy.

Taken as a whole, the cases treated according to their assayed needs responded well to immunologically guided therapy in 1943; twenty-four of twenty-six patients reported satisfactory resistance. Two failed for unaccountable reasons. A twenty-seventh patient, who was deliberately given less than her tentative PD, did not obtain her best result.

Unassayed Cases.—Among the eight patients arbitrarily given 10,000 units in 1943, seven reported satisfactory results. The incidence of excellent response here (two in eight) was, however, not as high as in the assayed class (Table III). The two unclassified individuals arbitrarily given 20,000 and 50,000 units reported good and excellent resistance respectively. They will be tried on 10,000 units next season.

COMPARISON OF CLINICAL RESULTS IN 1943 WITH THAT OF THE BEST PRECEDING YEAR UNDER TREATMENT

Assayed Group.—At the conclusion of the season, in 1943, the data for the most successful earlier year of secondary treatment were examined for each patient. In the case of the twenty-five patients who were given 10,000 units or less in 1943 because they had been classified as requiring no more, it was found that sixteen had reported excellent results in an earlier year and that nine had described their best preceding season as "good." As stated above, fifteen of this group obtained excellent results in 1943, and eight good. Thus, with two exceptions, the clinical behavior of 1943 resembled closely that of the individual's best earlier year under secondary therapy.

It is noteworthy that the total dose of the best preceding year was found to have exceeded 10,000 units in only three instances. (The year in question had been 1942 for all but three of the group of twenty-five cases.) Larger doses employed in still earlier years had failed to produce equally good relief. The greatest total dose given in any secondary course, other than that of 1943 and of the best preceding season, was found to have been 24,500 on the average. It varied from 6,500 to 110,000 units. Although the unusually high pollen concentration in the air during 1941 no doubt accounts for the relatively poor clinical resistance noted in that year, there were but seven patients who received their maximal dosage then. Ten of the remaining subjects took their greatest total doses in 1942, the others in 1939 and 1940—all years of about average pollination. Taking the first year of therapy into consideration, a somewhat higher average was found for the maximal dose of the group (32,000 units).

Ungraded Cases.—In the instance of the eight unassayed subjects given 10,000 units in 1943, a primary course had been taken by seven in 1942. Total dosage had ranged from 15,000 to 87,500 units. The influence upon clinical behavior had been excellent for four and good for four. In 1943, the response was somewhat less impressive—two excellent, five good, and one fair result. It remains to be shown whether

the incidence of satisfactory outcome will increase when these individuals are shifted from random dosage to immunologically guided therapy.

In general, the 10,000-unit course produced clinical immunity closely resembling that experienced after the most effective preceding therapy for the thirty-three members given this short course in 1943. There were seventeen excellent results and thirteen good ones as compared to twenty excellent and thirteen good responses among the best earlier years of the same group. This preceding season was not usually found to have been the one maximal dosage, which indicates that prolonged immunization carries no clinical advantage.

It seems possible that those who failed to reproduce their highest resistance in 1943 were incompletely immunized by means of cryochem-antigen. At the close of the season, cross-neutralization experiments revealed that at least one antigenic component had been destroyed by the freezing and drying procedure. Every patient who has subsequently been transferred from the dried antigen to our regular extract of comparable age has developed a generalized reaction in consequence. The unfavorable responses were seen even though the dose was reduced as much as 75 per cent at the time of transfer. These facts suggest that the missing component may play a role in the clinical allergy of most patients. It also proves the existence of more than one antigen in ragweed pollen.

THE EYE TEST, INTRACUTANEOUS TEST, AND SERUM ANTIBODY AS INDICES TO THE ADEQUACY OF TREATMENT

The Conjunctival Test.—We attempted to learn whether the threshold of reaction in the conjunctiva just before pollination might serve in any way to predict what degree of clinical resistance the booster course had built up in a patient. Among our subjects, satisfactory clinical results were obtained by all whose eyes, just before the season, gave no

TABLE IV

RELATION BETWEEN THRESHOLD OF CONJUNCTIVAL RESPONSE AND CLINICAL RESULT IN THIRTY-SEVEN PATIENTS GIVEN BOOSTER COURSES

THRESHOLD OF REACTION IN CONJUNCTIVA AFTER COURSE (PROTEIN NITROGEN UNITS)	CLINICAL RESPONSE	
	SATISFACTORY (NUMBER OF CASES)	UNSATISFACTORY (NUMBER OF CASES)
50	1	
75	1	
100	6	1
150	3	1
200	4	2
250	2	
300	5	
350	3	
400	5	
600	2	
2,500	1	

visible response to a drop of 250-unit extract. The clinical results associated with various thresholds of conjunctival response are indicated in Table IV. If the patient finished his course with a threshold response at 200 units or less, his behavior in the impending season of pollination could not be predicted since these thresholds were associated with fair, good, or excellent clinical results. The table shows that there were fifteen instances of satisfactory result and four of unsatisfactory among the group with these lower thresholds. These preliminary experiments justify further studies with the eye test as a crude barometer to the adequacy of therapy in the newly acquired patient. The details of these and other investigations along this line will be published shortly.[23]

A more reliable means of predicting the clinical prospects would be to observe the patient immunologically for one or more years. The degree of immunity found in the eye, skin, or blood during a successful season could then be taken as the minimal goal for future courses. Its absolute level, we found, varied somewhat with the individual. This applied even to the conjunctival test, where individual differences were less prominent than in the case of the other two tests. In the instance of the eye, tests had to be performed immediately before or after the hay fever season so as to avoid the possible complication of spontaneous ophthalmic hay fever.

The Intracutaneous Test.—The threshold of response in the skin at the end of the course also served to foretell in a limited way whether or not the patient would exhibit satisfactory clinical immunity. As shown in Table V, all of our patients whose skin required extract

TABLE V

RELATION BETWEEN INTRACUTANEOUS THRESHOLD AND CLINICAL RESULT IN THIRTY-FIVE PATIENTS GIVEN BOOSTER COURSES

INTRACUTANEOUS THRESHOLD AFTER COURSE (PROTEIN NITROGEN UNITS)	CLINICAL RESPONSE	
	SATISFACTORY (NUMBER OF CASES)	UNSATISFACTORY (NUMBER OF CASES)
0.000125	1	
0.0005	3	1
0.001	1	
0.01	9	1
0.1	6	2
0.5	2	
1	2	
2.5	2	
5	3	
10	2	

stronger than 0.1 unit per cubic centimeter to elicit a reaction after the booster course reported satisfactory seasons in 1943. There were eleven such cases. Among the patients with lower threshold requirements, there were four who recorded unsatisfactory clinical tolerance and twenty satisfactory. It would seem wise in the future to raise the

threshold to at least 0.5 unit if we wish to insure a good result in a newly acquired case. As soon as a patient has been observed through one successful season, the level of immunity found associated with this season can be taken as an individual guide to his future needs.

Titer of Thermostable Antibody in the Serum.—Eighteen patients who experienced excellent clinical control of their hay fever had developed antigen-binding powers which ranged from 550 to 3,750 PN units per cubic centimeter of serum by the time pollination began. The average preseasonal titer for these eighteen individuals was 1,621. For thirteen others, who estimated their clinical resistance as good, the titers ranged from 300 to 2,500, the mean being 1,271. The blood of four subjects with fair or poor results contained antibody capable of inactivating from 1,000 to 2,400 units of antigen per cubic centimeter of serum, the average for the four being 1,437.

Although the sizable group of patients reporting excellent response exhibited humoral immunity which was more marked in general than that of thirteen individuals with good results, the four unsatisfactory responders failed to show low titers in keeping with their behavior. The latter group was, of course, too small to be of statistical significance and it is also possible that unsuspected sensitivities contributed to their symptoms. Nevertheless, end points located by passive transfer could not in our experience be used with as much reliance as threshold tests of the eye and skin to predict the relative clinical resistance in a large group of patients. The reasons for this will be presented below.

DISCUSSION

The Short Booster Course.—Past investigations into the immunologic and clinical behaviors of pollen-allergic subjects have shown that optimal clinical protection can often be afforded by the administration of small amounts of extract to patients who have had at least one recent previous series of injections. After having individualized the preseasonal therapy of all patients for a number of years, we attempted to work out for 1943 a more uniform booster course which would meet the needs of our average patient in the shortest possible time consistent with safety. Analysis of the past courses and associated clinical results of the group revealed that a total dose of 10,000 PN units would probably be adequate, or more than adequate, for the needs of all but a few. Consequently, twenty-five individuals with an *estimated, tentative,* or *confirmed* protective dose of 10,000 units or less were limited to 10,000 PN units as a total dose for 1943. In twenty-three instances, the clinical response to this preseasonal stimulus was satisfactory. The same course was arbitrarily tried out on eight subjects whose immunologic needs had not been established. Seven of them manifested good or excellent general immunity during the ensuing season.

When these clinical results of 1943 were compared with those of the best earlier year of secondary therapy for the twenty-five individuals

(whom we had watched for several years), it was found that most of them had reported equally good results from doses of 10,000 units or less in 1942. In still earlier years, the preseasonal dosage had been greater, averaging 24,500 and ranging from 6,500 to 110,000 units; but the clinical benefit associated with these secondary courses had been no greater. Indeed, not infrequently, the effect had been less favorable. Excessive dosage appeared to be of no practical advantage to our patients.

The average number of hospital visits made by those on the 10,000 unit regime was 6.8, the average period of treatment, twenty-six days.

Generalized reactions provoked by the rapid booster series were in no instance severe. The incidence of 1 to each 11.8 visits can perhaps be reduced when the experimental phase of the booster regime has been completed. Our early attempts, reported herewith, to give each patient his allotted dose in the shortest possible period of time necessitated the use of maximal amounts of antigen each visit. It was not surprising, therefore, that the limits of tolerance were at times surpassed. The degree of overdosage was so little, however, that the resulting remote reaction could be described as "slight" in all but two instances. Recent analysis of the data suggests that some of these reactions might have been avoided had we not attempted to complete the 10,000-unit course in less than seven injections and had more leisurely courses been given to patients with marked conjunctival sensitivity.

The Pollen Count.—The fact that most cases reported optimal results in 1943 after taking the short booster course cannot be attributed to the fact that the pollination of ragweed in 1943 was slightly subnormal. Comparable control of symptoms had been reported by twenty-two of the twenty-five members of the group in 1942 after courses of 10,000 units or less. The ragweed pollen count for 1942 (1,641 grains per cubic yard of air for the entire season that ragweed was in bloom) was close to the average for the past fifteen years (1756).

Value of Tests as Immunologic Guides to Therapy.—Intracutaneous and conjunctival tests of the threshold type were compared with the passive transfer titration of serum antibody to determine which could best be used as aids (a) *before* a booster course to indicate what initial doses would be tolerated by a newly acquired patient, and (b) *at the end* of the course to show roughly whether immunization had been adequate. Of the three, the conjunctival test proved to be most helpful for both purposes. The threshold of response in the skin offered the second-best information, whereas the antibody titer of the serum came last in reliability.

The value of each of the tests was, however, greatly enhanced if the patient had been classified by their use in at least one preceding year, especially if satisfactory clinical resistance had been present. Under such circumstances, comparisons could be made between the current tests and the individual's own past responses rather than those of the

group. As in the case of the antibody titer of the serum, the degree of immunity found in the tissues of the skin and eye of clinically resistant patients varied somewhat with the individual. In interpreting the relation between these immunologic data and the clinical behavior, the rate of pollination, also, of course, had to be considered.

The Passive Transfer Test.—Earlier in this article, it was stated that the technique of passive transfer is less dependable than are cutaneous and ophthalmic tests for determining the relative refractoriness of the members of a sizable group. One reason for this is that end points vary widely with different test subjects. For reliable comparisons, only those titrations which are completed in the same subject can be employed. This automatically restricts comparisons to a small number of sera because only 5 to 10 samples can be evaluated in one subject, and the possibility of local immunity arises if the individual is employed repeatedly. Those who investigate the relationship between clinical and humoral immunity in hay fever must take into account this variable introduced by the test subject. If it can be shown that the in vitro method of Hampton, Johnson, Alexander, and Wilson[24] measures the same antibody as does the technique of passive transfer, its use may eliminate the difficulty under discussion.

When comparisons are restricted to end points found in the same experiment, some variation is still detected in the requirement of different individuals for thermostable antibody. In view of this finding, Cooke[25] reasons that "there is no basis for thus individualizing the protective nature of a protective antibody; that is, concluding that it varies for the patient rather than for the antigen." The writer feels that the clinical responses of two patients with equal antibody may depend, not on differences in the behavior of their thermostable antibody but on variance in the underlying sensitiveness of the two individuals. In other words, the amount of *reagin* may play an important role in determining the ultimate behavior. Or, assuming the reagin and antibody present in the blood and tissues to be identical for two individuals, their relative susceptibility to "H-substance" might be so different that a given contact with antigen might give rise to allergic symptoms in one and no manifestations in the other. That sensitiveness of different patients for a stated allergen varies in degree is clearly implied by the skin test classification of Cooke.[22] The wide range of reaction seen in our normal subjects when they are quantitatively tested with a uniform reagin-antigen mixture is another indication of individual difference in tolerance for "H-substance."

While recognizing that the clinical behavior of the allergic subject is influenced by numerous other factors, we feel that there is considerable evidence for the theory of a protective antibody in hay fever and that this evidence is in keeping with accepted immunologic concepts.

The Conjunctival Test.—The test which gave the most information was also the simplest of the three types employed. Its psychological

hazard was minimized by telling the subject that the point of the needle would be directed slightly *away* from his eye. By bringing the syringe upward from below, it was possible to make light contact between the hanging drop and the everted lower lid. Blinking was prevented by asking the subject to look toward the ceiling just before contact was made.

To exclude the possibility that the small amount of testing solution might lead to local immunization which would prejudice future tests, we irrigated the conjunctival sac with physiologic saline solution at the conclusion of the test. Epinephrine, 1:1,000, was finally instilled further to nullify the allergic reaction. A control experiment was done on one untreated patient to test the possibility of localized immunity. Nine threshold tests were performed without irrigations at intervals ranging from four to thirty-one days during a five and one-half month period. There was no indication of acquired local immunity.

Our experiments to date would seem to justify the following statement: short booster courses of pollen extract appear, within the limits of our experiment, to accomplish as much as prolonged, preseasonal treatments both from the immunologic and the clinical standpoints. Although the therapy is more intensive than that customarily employed by most allergists, it seems more conservative and practical than the "rush" inoculation method advocated by Freeman[26] of England. His system of giving multiple injections during a few days appears to bring satisfactory clinical results but carries the disadvantage of hospitalization. The risk of generalized reaction should be less when the course is spread out over several weeks, in our opinion, because time is thus given for the production of neutralizing antibody between doses.

PRECAUTIONS

It cannot be stressed too strongly that the booster principle discussed in this article must be applied with discretion. The individuals in our series had been under scrutiny for from one to five years. Their localized and generalized responses had been repeatedly studied by serologic, intracutaneous, ophthalmic and, in some instances, by nasal tests of quantitative nature. We were, therefore, thoroughly acquainted with the tolerance of each.

In future when the regime is to be tried on an immunologically unassessed patient, careful conjunctival and cutaneous tests will be performed to determine his sensitiveness. If freshly prepared solutions indicate a high degree of sensitivity, or if his history of past therapy suggests intolerance to dosage, conservative doses will be administered until his tolerance can be judged by his responses. Any dose which causes a localized reaction lasting over two and one-half days will be considered excessive.

Until we have had the opportunity to test a patient during a year when he is showing good clinical immunity, the preseasonal threshold

reactions found after his first booster course with us can perhaps be used as indices to his general resistance—comparison being made between his thresholds of response and those of the average patient. If his conjunctival sensitivity at the end of his booster course is such that extract stronger than 200-unit solution is required to elicit a threshold reaction, it seems probable from our limited experience that he will exhibit satisfactory clinical resistance during a season of average pollination in an area comparable to New York. The same statement applies to patients showing cutaneous thresholds above 1/10 unit at the end of the course. If the threshold doses lie below these figures, it will be our practice promptly to give a few more injections to heighten antibody production. Once the patient has been observed through a successful season, the threshold levels associated with this period will be adopted as the more desirable goals for his future treatment.

In closing it should be remarked that amounts of therapeutic antigen which suffice for patients in this area might prove inadequate for those in regions of more profuse pollination.

CONCLUSIONS

1. When ragweed-sensitive patients of the New York City area were given short booster courses which were suited to their immunologic needs, twenty-four of twenty-six acquired good or excellent clinical resistance.

2. For twenty-three of the twenty-six individuals, a secondary dosage of not over 10,000 protein nitrogen units afforded the satisfactory response.

3. After a total preseasonal, booster dose of 10,000 units, seven of eight unassessed cases obtained excellent or good clinical results.

4. The average patient tried on the 10,000-unit booster regime completed his course in twenty-six days and in 6.8 visits.

5. Since it was our aim to treat all patients as intensively as their tolerance permitted, generalized reactions occurred not infrequently. They were mild in degree and tended to appear in subjects who were either highly sensitive by conjunctival test or who were given the course in less than seven visits.

6. Threshold tests of the conjunctiva and skin prior to the booster course gave some indication as to which subjects would give generalized reactions during therapy. Tests repeated at the end of the course served as crude indices to the adequacy of therapy in newly acquired cases.

7. Once the patient had been carried through a season of satisfactory clinical behavior, the associated levels of tolerance found in his eye, skin or serum were adopted as the goal for his future therapy.

8. Future courses will be surrounded with every precaution against overstepping individual tolerance. Threshold tests will be carried out prior to therapy to assess the level of sensitiveness of each individual

so that initial doses may be suited to the tolerance. Careful attention will be paid to the localized reactions following therapeutic injections.

9. Within the limits of our experience, it appears that the booster principle can be applied to the preseasonal management of pollinosis with success. It usually leads to optimal immunologic and clinical results in minimal time without undue risk to the patient. The method is, however, still in the experimental stage and is not yet ready for general application.

10. The chief conclusion to be reached from our experiments is that immunologic guidance can advantageously replace the empirical management of hay fever. The opportunity is thereby afforded to avoid both over- and undertreatment.

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DISCUSSION

DR. JOSEPH WISEMAN.—I wish to present a small group of patients who were treated by the rapid injection method. It is a rather crude presentation in comparison with the meticulous work done by Dr. Loveless over a period of years. The following table describes the method and results:

A CLINICAL STUDY OF EIGHT RAGWEED HAY FEVER PATIENTS WHO HAD RECEIVED PREVIOUS RAGWEED TREATMENTS. INJECTIONS WERE STARTED JULY 16, 1943, AND DISCONTINUED AFTER THREE OR FOUR WEEKS

NUMBER	AGE (YR.)	SENSITIVITY	NUMBER OF MONTHS SINCE PREVIOUS RAGWEED INJECTION	NUMBER OF VISITS	NUMBER OF INJECTIONS	CONSTITUTIONAL REACTION	TOTAL RAGWEED EXTRACT IN TERMS OF .1 MG. NITROGEN PER C.C.	EQUIVALENT IN PROTEIN NITROGEN UNITS	RESULTS
1	37	B	7	9	15	0	7.446 c.c.	29,784	Good
2	14	AB	4	8	14	0	9.879 c.c.	39,516	Excellent
3	52	B	10	9	15	1	4.386 c.c.	17,544	Poor
4	51	B	9	7	12	3	1.656 c.c.	6,624	Excellent
5	11	C	11	6	13	0	7.766 c.c.	31,064	Excellent
6	45	A	10	8	15	1	4.001 c.c.	16,004	Fair
7	46	C	8	8	15	0	12.366 c.c.	49,464	Poor
8	47	A	4	4	10	0	1.96 c.c.	7,840	Poor
				59	109	5 (4.5%)			

Six patients have elected to repeat this treatment next year. Two have asked to return to perennial treatment. Case 8 cooperated poorly and only appeared four times. Usually three injections, one-half hour apart, were given at the first few visits. With increasing doses, the number of injections was reduced to two and then to one a visit.

STUDIES ON THE BLOCKING ANTIBODY IN SERUM OF RAGWEED-TREATED PATIENTS

II. Its Relation to Clinical Results

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In 1935, Cooke and his co-workers[1] demonstrated that the injection of ragweed antigen into ragweed-sensitive patients produced a new substance which they termed the "blocking antibody." Later, it was shown that a blocking antibody could be produced by the same means in normal, nonsensitive human beings[2] and in sheep.[3] Loveless, in 1940,[4] proved that this blocking antibody is thermostable. As we have previously reported,[5] we did not find the blocking antibody in other types of immune sera, such as convalescent pneumonia, measles, and scarlet fever serum.

The role of this blocking antibody in clinical results has been the subject of several studies. Loveless[6] demonstrated a rise in the blocking antibody titer in ragweed-sensitive patients during the course of treatment; and she believed that this rise corresponded with the degree of clinical improvement. Scully and Rackemann,[7] however, as a result of their studies, did not find any definite relation between clinical results and the blocking antibody titer; and Cooke,[8] in the discussion of their paper, agreed.

In 1943, Loveless[9] reported the clinical results in fifty-two ragweed-sensitive patients observed over a succession of pollinating seasons. She stated that when "the number of 'intensity hours' of hay fever for each was compared with the amount of thermostable antibody in his circulation during the season, a close parallel was found to exist between the amount of antibody and the degree of clinical insusceptibility in 79 per cent. Another 19 per cent of the group showed the correlation in all years but one, whereas one patient failed to show any connection between the two factors."

Since it seemed to be of prime importance to determine, from a fairly large series of cases, whether or not the concentration of immunologically demonstrated blocking antibody is proportional to clinical results, the present study was undertaken.

EXPERIMENTS

Series 1.—(Table I.) A preliminary study was undertaken in order to compare the blocking antibody titer in five ragweed-sensitive patients

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in May, before treatment was started, and again about the middle of August when the hay fever season was beginning and the patients had received ragweed therapy. Three untreated patients were used as controls.

As shown in Table I, there was a considerable increase in blocking antibody titer in every patient treated with ragweed antigen injections, whereas the untreated controls, tested at similar intervals, developed no such increase.

TABLE I

BLOCKING ANTIBODY BEFORE AND AFTER TREATMENT WITH RAGWEED

CASE	DATE	TOP DOSE OF RAGWEED ANTIGEN* (PROTEIN NITROGEN UNITS)	TOTAL DOSE OF RAGWEED ANTIGEN* (PROTEIN NITROGEN UNITS)	BLOCKING ANTIBODY TITER BEFORE TREATMENT (UNITS)	BLOCKING ANTIBODY TITER AFTER TREATMENT (UNITS)
O. S.	5/29/42	0	0	200	
	9/15/42	3,500	22,000	---	3,000
A. A.	5/27/42	0	0	150	
	9/19/42	1,500	10,000	---	800
I. R.	5/23/42	0	0	125	
	9/28/42	7,000	34,000	---	600
H. A.	6/ 1/42	0	0	300	
	9/17/42	5,000	32,000	---	3,000
E. K.	5/25/42	0	0	125	
	9/15/42	2,000	16,500	---	600
		Untreated Controls			
C. W.	5/25/42	0	0	100	
	10/ 1/42	0	0	150	
D. R.	5/23/42	0	0	100	
	8/24/42	0	0	100	
S. C.	6/ 1/42	0	0	200	
	8/17/42	0	0	200	

*Dose up to the time blood specimen was taken for antibody study. Treatment was not usually discontinued but reduced at this time, if not before.

While the neutralization titer of reaginic serum is often 75 units or less, that of the serum of the five cases studied before treatment in every instance was above this point. This difference probably was due to the presence of small amounts of blocking antibody in the reaginic serum of the five cases studied, and may be accounted for by the fact that these patients had received ragweed injections in preceding years, and all of them had received intracutaneous tests with ragweed extract.

Series 2.—(Table II.) In the second and larger group (thirty-four patients) treated in 1942 with ragweed antigen, blocking antibody titers were studied late in the hay fever season, in relation to (1) the total dosage of ragweed extract, (2) the clinical results, and (3) the years of previous treatment. All of these data are included in Table II.

Blocking antibody titers were determined by the neutralization technique. Clinical results were evaluated by comparing the severity of symptoms in the years before any treatment had been received with that exhibited during the 1942 season. The pollen count of the 1942

TABLE II

COMPARISON BETWEEN THE BLOCKING ANTIBODY TITER IN RAGWEED-SENSITIVE PATIENTS TREATED WITH RAGWEED EXTRACT AND (1) TOTAL TREATMENT DOSAGE, (2) CLINICAL RESULTS, AND (3) YEARS OF PREVIOUS TREATMENT

CASE	DEGREE OF SYMPTOMS AT PEAK OF HAY FEVER SEASON (AUGUST, 1942)	SKIN SENSITIVITY	YEARS OF PREVIOUS TREATMENT	TOP DOSE IN RAGWEED PROTEIN NITROGEN UNITS	TOTAL DOSE IN RAGWEED PROTEIN NITROGEN UNITS	UNITS OF BLOCKING ANTIBODY TITER	CLINICAL IMPROVEMENT (%)
1. F. G.	Marked	C	0	70	120	800	25
2. J. Z.	Marked	B	0	250	840	400	75
3. E. T.	Marked	C	0	1,600	5,200	1,000	90
4. P. K.	Moderate	A-B	0	1,000	4,360	600	35
5. C. G.	Marked	C	0	1,000	6,000	600	50
6. A. A.	Marked	B-C	0	1,500	10,000	800	50
7. E. K.	Marked	B	0	2,000	16,500	600	50
8. Q. J.	Moderate	C	0	3,500	17,500	600	85
9. J. M.	Marked	B	0	4,000	25,700	800	25
10. J. S.	Mod. mkd.	B	0	5,500	27,800	1,500	90
11. F. B.	Mild-mod.	C	0	6,500	32,900	600	50
12. P. G.	Mod. mkd.	B	0	6,000	43,600	800	90
13. S. B.	Moderate	B-C	0	5,500	47,000	600	80
14. N. S.	Marked	C	0	6,000	48,000	4,000	95
15. E. L.	Marked	B	0	10,000	147,500	800	25
16. T. C.	Marked	C	0	10,000	181,000	6,000	80
17. H. R.	Marked	B	6	1,500	5,400	600	60
18. A. F.	Moderate	C	5	4,300	17,300	800	80
19. M. B.	Marked	D	7	3,500	18,800	1,000	50
20. O. S.	Moderate	B	3	3,500	22,000	3,000	50
21. H. A.	Marked	B-C	3	5,000	32,000	3,000	50
22. I. R.	Mod. mkd.	C	3	7,000	34,600	600	15
23. R. K.	Marked	A-B	11	5,500	36,500	600	30
24. S. C.	Mod. mkd.	C	5	5,000	37,200	1,000	80
25. A. R.	Marked	B-C	1	8,000	45,300	2,500	50
26. V. H.	Marked	C-D	9	8,000	54,700	800	80
27. C. Y.	Moderate	C	8	9,000	55,000	1,000	50
28. H. G.	Marked	D	9	7,000	63,000	600	90
29. P. M.	Marked	C	5	12,000	103,000	4,000	50
30. D. L.	Marked	B	4	10,000	105,000	3,000	60
31. S. C.	Marked	C	4	9,000	111,500	3,000	50
32. J. W.	Marked	C	7	10,000	126,000	600	50
33. H. J.	Marked	C	6	10,000	140,000	800	75
34. A. P.	Marked	B	1	10,000	144,500	800	60
			Controls				
35. C. W.	Marked	C	1	0	0	150	50
36. C. W.	Mod. mkd.	A	1	0	0	600	35

season and the general severity of symptoms in nontreated patients during the hay fever season, in addition to the patients' own estimates of their relative symptoms, were taken into consideration. Such estimates, however, are always untrustworthy, for it is a matter of comparing an actuality with a recollection even though painstaking records are made.

PROCEDURE

A quantity of ragweed extract, in serial dilutions, was mixed with equal quantities of ragweed reaginic serum (one for each patient studied). This mixture was placed in the icebox for twenty-four hours or

more. Then 0.1 c.c. of each mixture (one for each serial dilution for each patient) was injected into the skin of subjects not sensitive to ragweed. Forty-eight hours later, 0.025 c.c. of ragweed extract, 1,000 protein nitrogen units per c.c., was injected into the same sites. Reactions were read fifteen to thirty minutes later, and it was determined at what dilution of antigen neutralization had taken place.

The blocking antibody titer of the serum from ragweed-treated patients was expressed by us in units of the antigen originally present in that site which, on subsequent testing, gave a negative or plus-minus response to the 1,000-unit dilution of antigen. This quantitative relation between the serum and the antigen representing the neutralization is taken roughly to indicate what Loveless[6] designates as the thermostable antibody titer.*

The immune sera were preheated to 60° or 62° C. for thirty minutes to inactivate the reagin, and were tested by passive transfer for evidence of loss of reaginic activity. A mixture of ragweed extract, reaginic serum, and physiologic saline was used as control.

In order to obtain a reaginic pool, sera from six ragweed-sensitive patients, not previously treated, were collected and pooled. Merthiolate, 1:10,000, was added as a preservative. This pooled serum was then tested for reaginic titer by means of the neutralization test. One-tenth cubic centimeter of each serial dilution of ragweed antigen was mixed with 0.1 c.c. of reaginic serum from the pool, plus an equal quantity of physiologic saline, in place of immune serum. Another similar mixture contained *immune* serum.

After incubation in the icebox for twenty-four hours, 0.1 c.c. of each mixture was injected into the skin of four recipients who were not sensitive to ragweed. Forty-eight hours later these sites were tested with 0.025 c.c. of 1,000 units of ragweed antigen and the neutralization point observed. A titer of 75 neutralizing units was recorded for the reaginic serum. Ragweed extract, as the antigen expressed in terms of protein nitrogen units, was used in serial dilutions ranging from 100 to 8,000 units per cubic centimeter.

As Loveless[9] has pointed out, the "thermostable antibody" response is highly individualistic. Table II amply illustrates the truth of this statement. For example, Case 1 with a total of 120 ragweed units of treatment, Case 6 with 10,000 units, Case 9 with 25,700 units, and Case 15 with 147,500 units, all produced a blocking antibody titer of 800 units. Also, an equal response was found in cases in which the top individual dose varied from 70 to 10,000 units. Moreover, Case 9, with a Class B skin sensitivity, after receiving 25,700 units with a top dose of 4,000 units, produced only 800 blocking antibody units, while Case 20, also with Class B skin sensitivity, after a total of 22,000 units and a top dose of 3,500 units, produced a titer of 3,000 units.

*Referred to by us as blocking antibody titer.

This pronounced variation in response to treatment indicates little correlation between the blocking antibody titer and the amount of treatment given. It will be observed that all blocking antibody titers rose after treatment, although the rise did not follow a consistent course and was not always proportional to the amount of treatment given.

In the present study, we have arbitrarily called a 75 per cent improvement or better, a "good" result; 50 to 75 per cent, a "fair" result; and below 50, a "poor" result. Our lowest blocking antibody titer in this series was 400 units. Therefore, we have considered 600 units and 800 units as relatively low titers, and 1,000 units or higher as relatively high.

By this system of measurement, 38 per cent of the patients who had "relatively high" titers had "good" results. However, since this percentage of good results was equalled by cases having "relatively low" blocking antibody titers, it would appear that good results are not dependent upon a high blocking antibody titer.

As to the influence of treatment in previous years, 50 per cent of those who had received such treatment developed high blocking antibody titers, and 50 per cent did not.

COMMENT

Loveless[9] has cited several patients followed for a number of years, who had good results from treatment in one season, increased clinical symptoms and reduced "thermostable antibody" titers in another when no treatment was given, and finally in another season of treatment a new rise in "thermostable antibody" and improvement of symptoms. From such observations she concluded that clinical results are proportional to the amount of "thermostable antibody." In cases in which a high titer was not accompanied by good clinical results, she believed the patient may have been reacting to some other allergens.

It has repeatedly been shown that ragweed injection helps 80 per cent or more of the patients treated; but not all of them receive the same amount of relief. It has also been demonstrated that ragweed injections produce blocking antibodies in treated patients. We do not believe, however, that these two results are necessarily related. In order to evaluate any possible relation between these results, it is necessary to determine what level of relief is to be compared with an arbitrary titer of blocking antibodies. Since but six of our thirty-four cases (17.6 per cent) obtained less than a 50 per cent improvement, we believe that, if high blocking titers are accompanied by good results, our patients who obtained 75 per cent or more relief should have had the highest titers. This was not the case. In the present study of thirty-four cases, thirteen patients showed a 75 per cent or better clinical improvement ("good" results); but only five of these had a relatively high blocking antibody titer (1,000 units or greater).

SUMMARY

The blocking antibody response has been studied in thirty-four cases of ragweed pollinosis treated with ragweed antigen. The results seem to warrant the following conclusions:

1. Ragweed antigen injections definitely produce specific blocking antibody titer in ragweed-sensitive patients.

2. Although high blocking antibody titers are to be found most frequently in patients who have received high total dosages of ragweed antigen, in the present study, 53 per cent of those who received high dosages did not develop high titers of blocking antibody.

3. Fifty per cent of the patients treated with ragweed antigen during previous years developed high blocking antibody titers.

4. Clinical results apparently do not depend upon high blocking antibody titers. The percentage of good results was identical in the patients who had low titers and in those who had high titers.

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ON THE ALLERGEN IN HUMAN DANDER

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IN A study of the allergenic interrelationship of various mammalian danders, human dander was used as a negative control. In one of the cases, however, this substance could not serve as a negative control because the patient gave a positive skin reaction to human dander, and her blood contained reagins for it. The reactions, both direct and passive transfer, could be repeated at will. The transfers were carried out with chemically clean syringes and the controls, in both sensitized and normal skin sites, were negative.

The subject of reactions to human dander is a controversial one. Most competent allergists doubt the existence of hypersensitiveness to human dander. They ascribe reports of positive reactions to the presence of nonspecific irritants in the dander and to technical errors.

Van Leeuwen and his co-workers[1-4] published the first reports on allergy to human dander. They found that it gave positive tests in most of their allergic patients and negative tests in others; therefore, they considered a positive reaction to this substance as indicative of the "allergic state." These findings were neither confirmed nor accepted by most American workers. The term, "allergic state," without further qualification, would today be considered indefinite, because it does not indicate the type of allergy, whether atopic allergy, contact type allergy, drug allergy, bacterial type allergy, etc.

Murphy and Cobe[5] called attention to the similarity between the skin reactions to human dander and histamine. The presence of a nonspecific irritant (or universal hypersensitiveness?) is undoubtedly the cause of much of the conflict in opinions on this subject.

Keller[6] reported positive skin reactions to dialyzed human dander extract in all of twenty-one cases of "spatexsudatives ekzematoid" (atopic dermatitis of adults). Controls in patients with other conditions were negative or the percentage of positive reactions was very low.

Hampton and Cooke,[7] using dialyzed, standardized extracts, found that a high percentage of patients with dermatitis ("eczema," presumably of the atopic type) gave positive skin tests to, and had reagins for, human dander, whereas, in other manifestations of allergy, the incidence of skin reactions and of reagins was very much less. These

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authors also found partial cross neutralization between human dander and house dust, but found no cross relationship between reactions to human dander and other mammalian danders.

EXPERIMENTAL

Materials and Methods.—Combings of dander from the scalp, superficial scrapings of normal and diseased human skin, and other substances, as indicated, were used (Tables I and II). Extracts were made in 50 per cent glycerin, using a volume of fluid approximately twice that of the loosely packed material to be extracted. Oily substances were removed first with ether. Neither filtration nor any other standardization was used for the extracts for direct testing, which was done by the scratch method. For the passive transfer tests, intradermal injections of 1:100 carbolized buffered saline dilutions of centrifuged extracts were employed. (The quantities involved were usually so small that Seitz filtration would have involved large percentage losses of active material by adsorption to the filter.) Previously unused, or otherwise chemically clean, syringes were used for neutralization and passive transfer tests.

Skin Reactions to Direct Tests.—Skin tests were performed on fifty selected persons with eight preparations. The substances used, together with the reasons for their use, were as follows:

1. Human dander from the scalp of normal adults; this was the substance under investigation.

2. Epidermis from the sole of the foot of normal adults; in order to study the reaction to cornified epidermis without hair or products of sebaceous glands or hair follicles.

3. Epidermis from the arms and legs of a newborn infant (stillborn); to obtain the reaction of epidermis relatively free from bacterial and other external contaminants.

4. Vernix caseosa; because of its possible relationship to epidermis and because of absence of external contaminants.

5. Scrapings from the lesions of seborrheic dermatitis; because of the clinical association of this condition with excessive dander of the scalp.

6. Scales of exfoliative dermatitis; because they furnish an abundant source of epidermis from the general body surface.

7. Human serum (negative control).

An effort was made to obtain dander from the scalp of a newborn infant, but all the newborn infants examined were found to be free from dander.

The purpose of these tests was chiefly to obtain additional dander-sensitive patients for further study, although a comparison of the reactions to the eight substances listed was expected to yield some additional information.

TABLE I

DIRECT SKIN TESTS WITH HUMAN DANDER AND OTHER SUBSTANCES

CASE NUMBER	CLINICAL DIAGNOSIS	AGE OF PATIENT	HUMAN DANDER (SCALP)	SEBORRHEIC DERMATITIS SCALES	PSORIASIS SCALES	EXFOLIATIVE DERMATITIS SCALES	EPIDERMIS OF NEWBORN INFANT	VERNIX CASEOSA	EPIDERMIS FROM SOLE OF FOOT	HUMAN SERUM
1	Atopic dermatitis	12 yr.	+++	+	-	-	-	-	-	-
2	Atopic dermatitis	19 yr.	±	-	-	-	-	-	-	-
3	Atopic dermatitis	35 yr.	-	-	-	-	-	-	-	-
4	Atopic dermatitis	4 mo.	-	-	-	-	-	-	-	-
5	Atopic dermatitis	3 mo.	±	-	-	-	-	-	-	-
6	Atopic dermatitis	25 yr.	±	-	-	-	-	-	-	-
7	Atopic dermatitis	8 mo.	-	-	-	-	-	-	-	-
8	Atopic dermatitis	30 yr.	-	-	-	-	-	-	-	-
9	Atopic dermatitis	14 yr.	±	-	-	-	-	-	-	-
10	Atopic dermatitis	13 yr.	+	+	-	-	-	-	-	-
11	Atopic dermatitis	3 mo.	±	±	-	-	-	-	-	-
12	Atopic dermatitis	4 mo.	-	-	-	-	-	-	-	-
13	Atopic dermatitis	24 yr.	+	+	-	-	-	-	-	-
14	Atopic dermatitis	24 yr.	-	-	-	-	-	-	-	-
15	Atopic dermatitis	26 yr.	+++	++	-	-	-	-	-	-
16	Atopic dermatitis	22 mo.	±	±	-	-	-	-	-	-
17	Atopic dermatitis	21 yr.	+++	++	-	-	-	-	-	-
18	Atopic dermatitis	12 yr.	+	+	-	-	-	-	-	-
19	Atopic dermatitis	17 mo.	±	±	-	-	-	-	-	-
20	Atopic dermatitis	21 yr.	++	+	-	-	-	-	-	-
21	Atopic dermatitis	21 yr.	++	+	-	-	-	-	-	-
22	Atopic dermatitis and hay fever	30 yr.	±	±	-	-	-	-	-	-
23	Atopic dermatitis and hay fever	11 yr.	+	±	-	-	-	-	-	-
24	Asthma	20 yr.	-	-	-	-	-	-	-	-
25	Asthma	52 yr.	+	±	-	-	-	-	-	-
26	Asthma	40 yr.	-	-	-	-	-	-	-	-
27	Asthma	62 yr.	-	-	-	-	-	-	-	-
28	Asthma	38 yr.	±	-	-	-	-	-	-	-
29	Asthma	39 yr.	±	-	-	-	-	-	-	-
30	Asthma	17 yr.	-	-	-	-	-	-	-	-
31	Asthma	22 yr.	±	-	-	-	-	-	-	-
32	Hay fever	18 yr.	-	-	-	-	-	-	-	-
33	Hay fever	28 yr.	-	-	-	-	-	-	-	-
34	Hay fever	32 yr.	±	-	-	-	-	-	-	-
35	Hay fever	27 yr.	-	-	-	-	-	-	-	-
36	Hay fever	32 yr.	±	-	-	-	-	-	-	-
37	Hay fever	38 yr.	±	-	-	-	-	-	-	-
38	Hay fever and asthma	35 yr.	±	±	-	-	-	-	-	-
39	Hay fever and asthma	19 yr.	±	±	-	-	-	-	-	-
40	Hay fever and asthma	12 yr.	-	-	-	-	-	-	-	-
41	Normal adult	44 yr.	±	±	-	-	-	-	-	-
42	Normal adult	37 yr.	-	-	-	-	-	-	-	-
43	Normal adult	28 yr.	+	-	-	-	-	-	-	-
44	Normal adult	22 yr.	-	-	-	-	-	-	-	-
45	Normal adult	42 yr.	-	-	-	-	-	-	-	-
46	Normal adult	38 yr.	-	-	-	-	-	-	-	-
47	Normal adult	52 yr.	±	±	-	-	-	-	-	-
48	Normal adult	29 yr.	±	±	-	-	-	-	-	-
49	Normal adult	30 yr.	±	-	-	-	-	-	-	-
50	Normal adult	26 yr.	-	-	-	-	-	-	-	-

TABLE II

DIRECT (SCRATCH) AND PASSIVE TRANSFER (INTRACUTANEOUS) TESTS ON FIVE PATIENTS ALLERGIC TO HUMAN DANDER

TEST	DIR.	TRAN.	DIR.	TRAN.	DIR.	TRAN.	DIR.	TRAN.	DIR.	TRAN.
CASE NUMBER	1		15		17		20		21	
Human dander, adult scalp	+++	+++	+++	+++	++	+++	++	+++	++	++
Human dander, scalp of nun 1	+	++	+	+	++	++	+	+	+	+
Human dander, scalp of nun 2	+++	+++	+++	+++	++	+++	++	+++	++	++
Human hair, adult, scalp 1	±	++	++	+	++	++	+	+	++	++
Human hair, adult, scalp 2	+	++	±	+	+++	+++	++	++	++	++
Human hair, adult, scalp 3	+	++	±	++	++	++	+	+	+	+
Human hair, adult, scalp 4	–	–	–	–	–	–	–	–	–	–
Human hair, adult, scalp 5	+	+	±	+	±	+	–	±	–	–
Human hair, adult, pubic	–	±	–	±	±	+	±	±	–	–
Human hair, adult, axillary	–	–	–	–	–	–	–	–	–	–
Human hair, adult, thigh	–	–	–	–	–	–	–	–	–	–
Human hair, 1-year-old child, scalp	–	–	–	–	–	±	–	±	–	–
Human hair, 5-month-old child, scalp	–	–	–	–	–	–	–	±	–	–
Human hair, newborn infant 1, scalp	–	–	–	–	±	±	–	±	–	±
Human hair, newborn infant 2, scalp	–	–	–	–	–	–	–	–	–	–
Human hair, newborn infant 3, scalp	–	–	–	–	–	–	–	–	–	–
Human hair, newborn infant 4, scalp	–	–	–	–	–	±	–	–	–	–
Human hair, newborn infant 5, scalp	–	–	–	–	–	–	–	–	–	–
Human hair, newborn infant 6, scalp	–	–	–	–	–	–	–	–	–	–
Human epidermis, newborn infant, arms and legs	–	–	–	–	–	–	–	–	–	–
Human epidermic, sole of foot, adult	–	–	–	–	–	–	–	–	–	–
Sebaceous cyst, hair	–	–	–	–	–	–	–	–	–	–
Sebaceous cyst, wall	–	–	–	–	–	–	–	–	–	–
Sebaceous cyst "fluid" (ether residue)	–	–	–	–	–	–	–	–	–	–
Seborrheic dermatitis scales, Case 1	+	++	±	+	++	++	+	+++	+	+++
Seborrheic dermatitis scales, Case 2	+	++	±	++	+	++	+	++	+	++
Psoriasis scales	–	–	–	–	–	–	–	–	–	–
Exfoliative dermatitis scales	–	–	–	–	–	–	–	–	–	–
Cryptococcus	–	–	–	–	–	–	–	–	–	–
Pityrosporum ovale	–	–	–	–	–	–	–	–	–	–
Staphylococcus albus 1	–	–	–	–	–	–	–	–	–	–
Staphylococcus albus 2	–	–	–	–	–	–	–	–	–	–
Diphtheroid bacillus	–	–	–	–	–	–	–	–	–	–
Sarcina	–	–	–	–	–	–	–	–	–	–
Large gram-negative bacillus	–	–	–	–	–	–	–	–	–	–
Staphylococcus aureus 1	–	–	–	–	–	–	–	–	–	–
Staphylococcus aureus 2	–	–	–	–	–	–	–	–	–	–
Staphylococcus aureus 3	–	–	–	–	–	–	–	–	–	–
Large gram-negative spore-forming bacillus	–	–	–	–	–	–	–	–	–	–

RESULTS

1. The extracts of human scalp dander and, to a lesser extent, that of seborrheic dermatitis lesions were found to be slightly reactive in the

majority of skins tested, both in patients and normal adults. This reactivity was manifested by a very small wheal and often slight erythema, very slightly but perceptibly larger than that produced by the control scratch. The other five substances gave negative reactions (Table I).

2. In five patients, all with atopic dermatitis, the reactions to human dander and to seborrheic dermatitis scales were positive (Table I). These five patients were selected for further study.

Local Passive Transfer Reactions.—Passive transfer reactions to human dander were obtained with the sera of each of these five patients. The controls in normal skin sites were negative and the saline controls in sensitized sites, likewise, were negative. The same results were obtained with three different specimens of dander. Scales of seborrheic dermatitis gave similar, but smaller, reactions.

STUDY OF THE BIOLOGIC ORIGIN OF THE ALLERGEN

The existence of allergic activity in human dander is to be regarded as having been established by previous investigators and confirmed by the present studies. The next problem was to investigate the source and nature of the allergen because these might have a bearing upon its possible clinical significance and upon the problem of allergy to products derived from the patient's own tissues (Hecht, Sulzberger, and Weil.[8]). The following sources were considered: (1) particulate matter suspended in the air, such as house dust, orrisroot, wool, silk, cotton, feathers, pollen, etc.; (2) bacteria, fungi, or other microorganisms growing on the scalp; (3) stratified squamous epidermal cells from the scalp; (4) cells from the hair or hair follicles; and (5) secretion of sebaceous glands.

These possibilities were investigated as follows: Direct skin tests were performed on the five patients with extracts of various substances in order to determine whether or not a correlation existed between the reactions to human dander and any other substance or substances. These tests included: (1) one hundred and ninety-two common foods and inhalants (including house dust, feathers, cottonseed, wool, silk, orrisroot, karaya gum, and many pollens); (2) eleven microorganisms cultured from the scalp (Tables I and II) (on plan agar, blood agar, and Sabouraud's media); (3) dander from the scalp of two persons who keep their heads covered with cloth day and night (two nuns who sleep in nightcaps); (4) hair from the scalps of several adults and children; (5) hair from six newborn infants (presumably with a minimum of contamination by microorganisms or by various dusts from the air); (6) pubic hair; (7) axillary hair; (8) hair from the thigh; (9) epidermis from arms and legs of a newborn (stillborn) infant; (10) hair, fluid, and inner cyst wall from a dermoid cyst* (free from micro-

*Dermoid cyst of the ovary, supplied by Dr. A. J. Miller, Pathologist, University of Louisville, School of Medicine.

organisms and other external contaminants); and (11) scales from the lesions of psoriasis, exfoliative dermatitis, and seborrheic dermatitis.

Local passive transfer tests were performed with the substances named above. Antibody neutralization studies (in vitro) were carried out in order to determine whether or not any other substance would cross react with human dander (neutralize the dander antibody).

RESULTS

CASE 1.—The patient gave positive reactions to human dander and scalp hair, and dog dander; slightly positive reactions to seborrheic dermatitis scales, and to several foods and inhalants. Both human and dog dander transferred well. Neither neutralized reagins for the other. Testing of this patient is incomplete because she moved from the city.

CASE 2.—This patient gave positive reactions to human dander and scalp hair; slightly positive reaction to seborrheic dermatitis scales. None of the common inhalants or foods gave a definitely positive reaction. Antibody neutralization was attempted, nevertheless. House dust, orrisroot, bluegrass pollen, feathers, silk, wool, ragweed pollen, and cottonseed failed to neutralize reagins for human dander.

CASE 3.—This patient gave positive reactions to human dander, human hair from the scalp (slightly positive to pubic hair), seborrheic dermatitis scales, house dust, feathers, wool, silk, egg, and pork. Antibodies for human dander were not neutralized by house dust, feathers, wool, silk, egg, or pork.

CASE 4.—This patient gave positive reactions to human dander, human hair from the scalp and pubic hair, seborrheic dermatitis scales, silk, ragweed pollen, karaya gum, several fungi, and foods. None of the inhalants or foods neutralized reagins for human dander. (Neutralization not attempted with scalp or pubic hair, or seborrheic dermatitis scales.)

CASE 5.—This patient gave positive reactions to human dander, human scalp hair, seborrheic dermatitis scales, ragweed pollen, horse and cow dander, house dust, and several foods. Antibodies for human dander were not neutralized by any of the other substances (except human hair and seborrheic dermatitis scales) (Table II).

DISCUSSION

The origin and nature of the allergen are of theoretical and, perhaps, clinical importance. The reason for believing that the allergen is not a constituent present in stratified squamous epidermis in general is the following: patients who give skin reactions to human scalp dander and human scalp hair do not react to epidermis from the general body surface of an adult and of a newborn infant; to scalp hair from a newborn infant; to hair, sebaceous material, and inner lining of a dermoid cyst; or to scales from the lesions of psoriasis and exfoliative dermatitis.

The reasons for believing that the allergen does not have its origin in accidental contamination of dander with suspended dust particles from the air are:

1. Patients who react to skin tests with human scalp dander and hair react to the same degree to dander obtained from persons whose scalps are kept covered almost continuously, day and night.

2. Reagins for human dander are not neutralized by the common atmospheric dust particles.

3. There is no constant correlation between the reactions to human dander and atmospheric dusts.

The fact that patients who are allergic to human dander give positive skin reactions also to the scales of seborrheic dermatitis obtained from the face, neck or elsewhere is in agreement with the clinical observation that this disease is often associated with excessive dander.

The allergen of human dander may occur in the desquamated epidermal cells of the scalp as the result of some physiologic maturation process specific for the scalp epidermis. It is also possible that the allergen may have its origin in some microorganism living, but not always pathogenic, on the scalp. This hypothetical microorganism (not obtained in my cultures from the scalp) may, under certain circumstances, become pathogenic and result in the disease, seborrheic dermatitis. In fact, it is possible that these findings may be of as much importance for the study of the nature of seborrheic dermatitis as they are for atopic dermatitis.

The reasons for the microorganism theory of origin are chiefly of a negative character, namely, (1) suspended atmospheric dust particles are excluded for the reasons enumerated above, and (2) while hair from the adult scalp, with its opportunity for contact with microorganisms, elicits reactions, hair from the scalp of a newborn infant and hair and other constituents of a dermoid cyst fail to produce reactions.

SUMMARY

1. The existence of allergy to human dander is an established fact.

2. The clinical significance of this fact remains to be investigated.

3. Our present knowledge warrants only the conclusion that this allergy is often associated with atopic dermatitis; that while in some cases it may possibly be of etiological significance, in many other cases it is, quite possibly, merely a concomitant, subclinical sensitivity.

4. The experimental data here presented suggest that the human dander allergen is present also in scales of seborrheic dermatitis, but absent in numerous other scales and other materials.

5. The significance of these findings in relation to some problems of seborrheic dermatitis is discussed briefly.

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STUDIES IN FOOD ALLERGY*†

III. Sensitization to Fresh Fruits. Immunochemical Aspects

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IN A PREVIOUS communication, a labile antigen was shown to exist in many fresh fruit extracts. Deterioration of that antigen was found to be greatest within the first twenty-four hours, and became complete in most instances within three days. The antigen was also thermolabile, being altered or destroyed by heat. Rapid freezing on the other hand, preserved its allergenic properties. Seitz filtration reduced the potency of the freshly extracted juices.

We next sought to determine the possible reasons for the deterioration of fresh fruit extracts. Several explanations for this phenomenon occurred to us. Thus, one could postulate the existence of an unstable allergen which was readily altered by oxidation. This supposition would account for the preservation of allergenic activity in the frozen fruit and for the length of time needed for the complete deterioration. It would fail however to explain the reduction of antigenicity by Seitz filtration, although this probably is due to adsorption of the protein molecules by the filter pad, as occurs, for example, after filtration of certain sera and of bacteriophage.

A more plausible explanation presupposed the existence of a proteolytic enzyme in the fresh fruit. Such an enzyme might be held in check in the intact fruit by an enzymase which in turn is oxidized on exposure to air thus allowing the enzyme to act upon and, thus, alter the active allergenic principle. We found a parallelism for such a theory in studies done with pineapple and papaya.[2] Thus, two proteolytic enzymes, termed papain and chymopapain, have been prepared in the crystalline state from the green papaya.[3] Drying of the fresh papaya latex caused much of the enzyme to disappear.[4] This disappearance is due partly to the loss of another substance that serves as an activator of the enzyme from the latex. The chemical constitution of this activator is not known, but it contains an organic sulfide group and is a reducing agent. The activator appears to keep the enzyme in a reduced condition, for, if the enzyme is oxidized, it becomes inactive. It may be reactivated by the addition of this natural activating substance or by the addition of many chemicals that are good reducing agents. Among the substances that may be used for this purpose are cysteine, sulfites, alkaline cyanides, and sulfides, the last two being extremely poisonous chemicals. Almost

*From the Clinic of Allergy and Applied Immunology, Temple University Hospital and Medical School.

†Read before the American Association for the Study of Allergy, Atlantic City, New Jersey, June 8, 1942.

any good reducing agent that does not destroy proteins can serve as an activator of papain. Exposure to air probably inactivates papain because the enzyme is oxidized. The addition of salt to the moist latex seems to prevent a loss of enzymatic activity.

Bromelin[5] is the name given to the proteolytic enzyme obtained from pineapple. Its action is aided by the presence of reducing agents like hydrogen sulfide, cysteine, sodium cyanide, or the natural activator of the enzyme present in the pineapple. This enzyme has never been prepared in a pure state.

In view of these factors, it seemed likely that similar enzymatic substances might exist in other fresh fruits. If their existence could be proved, it might serve to explain the antigenic deterioration that occured in fresh fruit extracts. Studies were therefore undertaken to investigate the various possibilities, and the results obtained are the subject of the present report.

METHODS OF PROCEDURES

Our chief difficulty at first was in the procurement of proper clinical material. Fortunately, we had a patient (Case 4) clinically sensitive to peaches, who volunteered to act as our subject. Unless otherwise specified, all other experimental investigation herein reported refers to work done with the peach extract. Likewise, any reference to skin tests includes those done directly upon the patient and those done by passive transfer on at least two nonallergic subjects.

Preparation of Fruit Juice.—Juice from fresh, ripe peaches was obtained by squeezing and crushing the whole fresh fruit through sterile cheesecloth and cotton gauze. The juice from frozen peaches was obtained by permitting them to thaw, then washing with distilled water to remove sera, and finally by passage through cotton gauze.

All juices were centrifuged to remove particles of fruit and the supernatant fluid was employed in the tests.

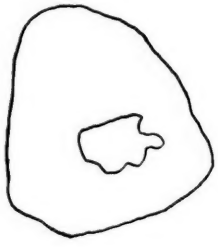
The tests were carried out as soon as possible after the preparation of the juices in order to avoid deterioration of any labile substances which might be present.

BIOCHEMICAL STUDIES

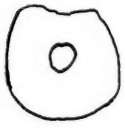
A. *Precipitation of Protein Nitrogen Fraction.*—The active (protein nitrogen) fraction of the peach extract was obtained by precipitation with sodium tungstate. Four cubic centimeters of water, 1 c.c. of 10 per cent sodium tungstate, and 1 c.c. two-thirds normal sulfuric acid were added to 1 c.c. of freshly extracted peach juice. The mixture was agitated by tapping and then centrifuged at a high speed for ten minutes. The filtrate was drained off. One drop of 10 per cent sodium hydroxide was added to the precipitate. Sufficient water was added to bring the solution to its original volume (1 c.c.). The potency of the extract thus obtained was compared to the freshly extracted peach juice

by means of direct skin tests and passive transfer performed at regular intervals after extraction. We hoped in this way to separate the substance causing the deterioration from the active protein nitrogen portion, and thus stabilize our extract.

The active protein nitrogen fraction of the peach extract was successfully recovered after precipitation with a 10 per cent sodium tungstate solution. This fact was demonstrated by its ability to produce markedly positive reactions in the patient clinically sensitive to peaches as well as in the passively transferred site (Fig. 1). The rate of deterioration, however, was similar to that of the unaltered juice. Marked diminution in the allergic properties of the solution took place in three days and total loss of activity in six days (Fig. 2). Apparently, the substance causing the deterioration was precipitated along with the protein nitrogen fraction.



Freshly prepared solution



Solution 3 days old

Fig. 1.

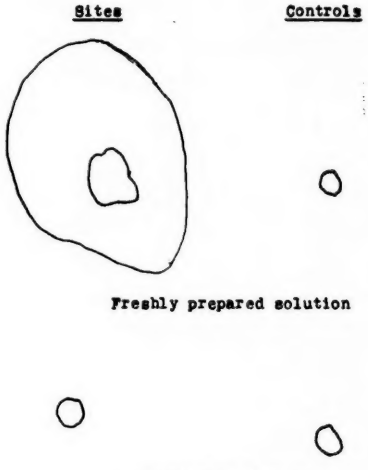


Fig. 2.

Fig. 1.—Direct skin tests on D. H. using a solution of peach protein nitrogen that was precipitated with phosphotungstic acid.

Fig. 2.—Passive transfers with D. H. serum; testing with peach protein nitrogen solution that was precipitated by phosphotungstic acid.

B. *Inhibition of Enzymes.*—Many enzymes are inhibited by oxidation and by the addition of sodium cyanide. If the deterioration is due to enzymatic activity, then the inhibition of these enzymes might result in a more stable extract. Freshly extracted peach juice was oxidized by bubbling air through the solution for one hour. To another portion, sufficient sodium cyanide was added to make the resultant solution contain 0.25 per cent sodium cyanide. These solutions were tested for activity immediately after preparation. Retests were made at regular intervals, thereafter, to note the degree and the rate of deterioration.

The solutions subjected to prolonged oxidation showed a partial loss of allergenic activity. This was demonstrated by direct skin tests on the sensitive patient immediately after the solution had been prepared. Deterioration was complete within six days (Fig. 3). Passive transfer studies with these solutions showed essentially the same results (Fig. 4).

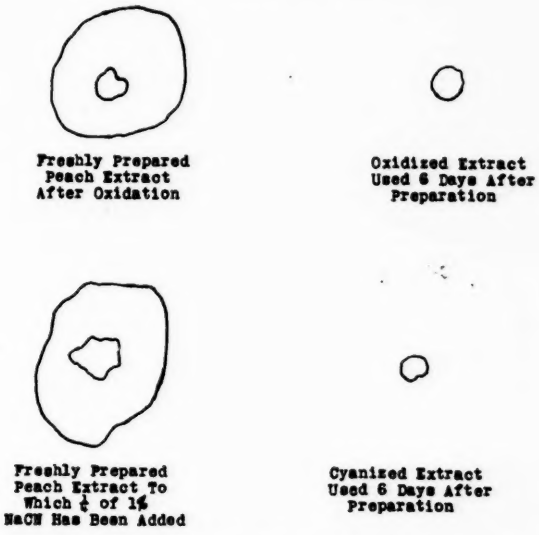


Fig. 3.—Direct skin tests on D. H.

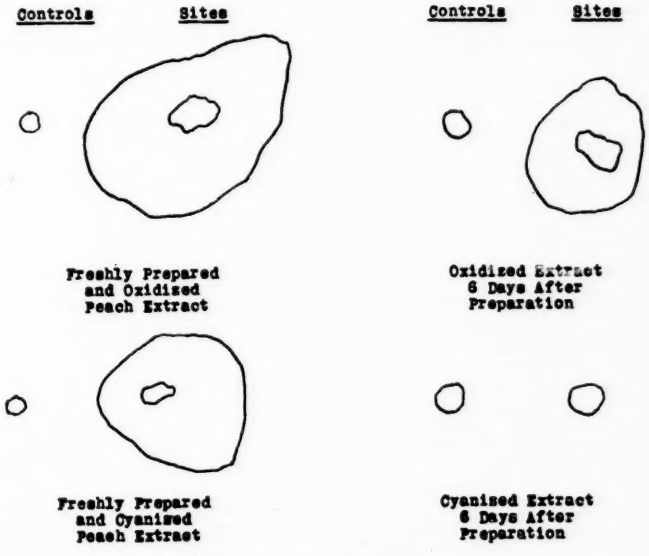


Fig. 4.—Passive transfers with D. H. serum.

The addition of 0.25 per cent sodium cyanide failed to alter the rate of deterioration in the fresh fruit extract. There was little or no alteration in its allergenic activity immediately after preparation, as shown

by direct skin tests on the sensitive individual (Fig. 3). There was, however, complete loss of antigenicity within six days. Similar results were obtained with the cyanized extract in the passively transferred sites (Fig. 4).

C. *Variations in pH of Extracts.*—Most enzymes require an optimum pH for maximum activity. Thus, pepsin requires an acid medium for its activity while trypsin requires an alkaline one. If loss of antigenicity was due to enzymatic activity, it seemed possible that the activity could be altered by varying the pH of the solutions. The pH of freshly extracted peach juice was determined by chemical indicators. Tenth-normal hydrochloric acid or sodium hydroxide was then added to make one solution acid, one neutral and one alkaline. These solutions were tested by direct skin tests and by passive transfer at regular intervals after preparation.

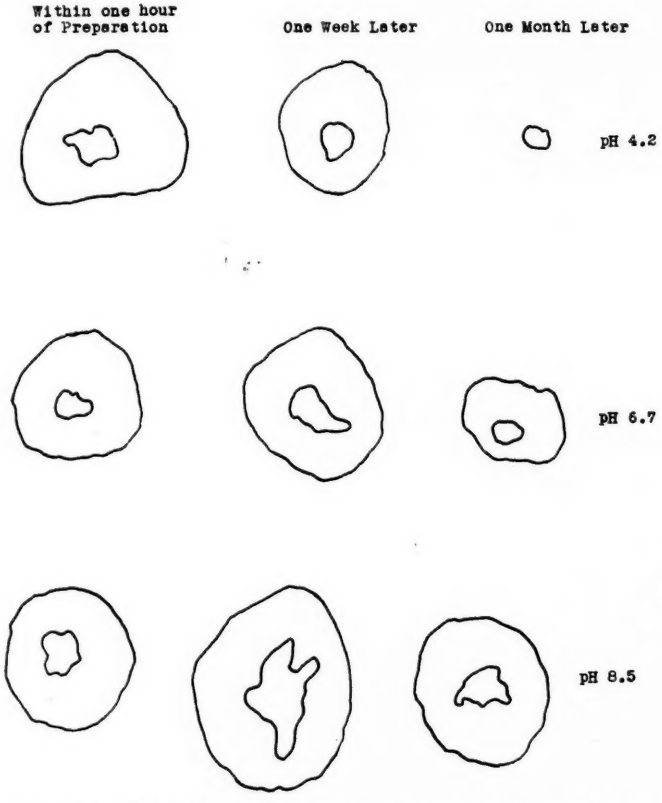


Fig. 5.—Direct skin tests on D. H. with 1:5 dilution of peach extract.

Numerous determinations of the pH of freshly extracted peach juice gave figures varying between 4 and 5.1. The addition of tenth-normal sodium hydroxide to render the solution neutral or alkaline yielded one which gave irritating and nonspecific skin reactions upon injection. This was obviated by using a 1:5 dilution of the concentrated solution which

eliminated this tendency. All the pH studies subsequently referred to were conducted, therefore, with the 1:5 dilution of the original extract. The pH determinations on the solutions thus prepared showed values of 4.2, 6.7, and 8.5.

The unaltered peach juice with a pH of 4.2 showed the most rapid deterioration; the neutralized solution with a pH of 6.7 showed retention of allergenic activity for a longer period of time; whereas the alkaline extract pH 8.5 retained its antigenicity for over three months (Figs. 5 and 6). This showed that the rate of deterioration could be altered by changing the pH of the solution. In the case of peach extract a pH of 8.5 seemed most favorable for the retention of the allergenic activity.

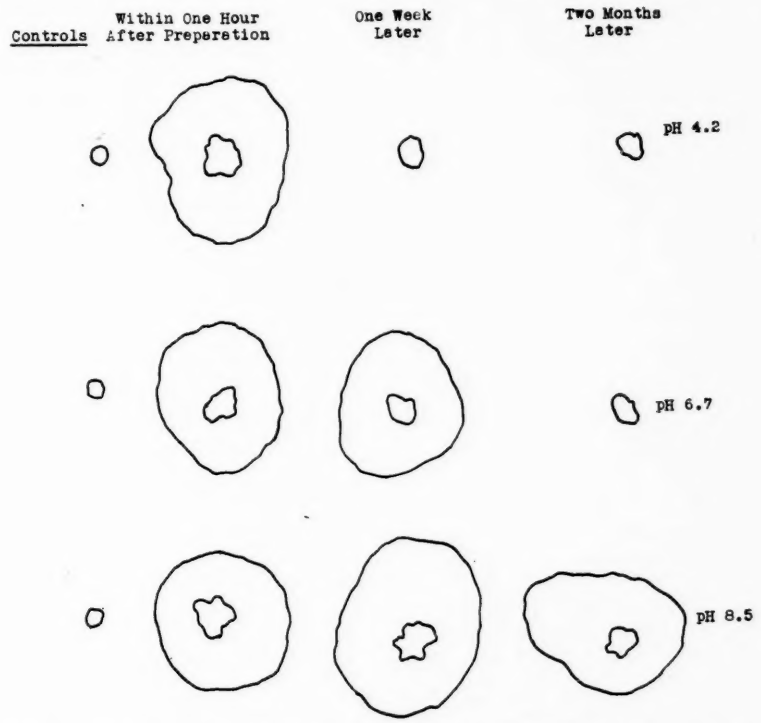


Fig. 6.—Passive transfers using D. H. serum, and testing with 1:5 dilution of peach extract.

D. *The Effect of Lyophilization.**—Attempts were made to preserve the allergenic activity of freshly extracted peach juice by the process of lyophilization. Some extracts were acidified to pH 4 and some were alkalinized to pH 8.5 before being lyophilized. After aging the lyophiled extract for varying periods of time (up to six months), they were restored to their original volume by the addition of sterile distilled water. They were then tested for activity by direct skin tests and passive transfer.

*Lyophile extracts were prepared through the courtesy of Sharp and Dohme, Inc.

The lyophile extract preparation was not considered satisfactory since the resultant product was either a crystallike mass or a gummy substance instead of a dry porous powder. Neither of these preparations took up water as readily as a good lyophile preparation.

The lyophile extract was restored to its original volume and then diluted, 1:5. Positive skin reactions of the same magnitude as in the unaltered extract were obtained with these extracts. The rate of deterioration of the acid extract (pH 4) was quite rapid, with complete loss of activity in three days. The activity of the alkaline extract lasted four weeks. Lyophilization could, therefore, be used as a source of supply for active extracts when fresh fruits are not available. It did not alter the rate of deterioration when the lyophile was put back in solution.

E. *Addition of Reducing Agents.*—Drying of papaya and pineapple causes a loss of the enzymes contained in these fruits. Reactivation of these enzymes may be accomplished by the addition of reducing agents. We were interested, therefore, in determining whether reducing agents would have a similar effect on the allergenic properties of peach extract.

Sodium bisulfite, sodium cyanide, and sodium sulfide, in concentrations of 0.1 and 0.25 per cent, were added to both the freshly prepared peach extract and to an eight-day-old extract that had lost its ability to produce positive skin reactions in the test subject.

When tested one day later there was no evidence of restoration of allergenic activity in the deteriorated extract. The addition of these reducing agents also failed to modify the deterioration in the freshly prepared extract.

DISCUSSION

While our investigations have failed to discover the actual cause of the deterioration of the fresh fruit extracts, they have, nevertheless, given us a little better insight into its possible character. The fact that the protein nitrogen precipitate carried with it the substance responsible for the deterioration shows that the active allergenic principle is in close association with the protein nitrogen fraction. We suspected that the substance responsible for the allergenic activity might be an enzyme present in the protein fraction. Attempts to inhibit the activity of such an enzyme by oxidation or by reducing agents which are effective with the enzymes of papaya and pineapple were unsuccessful in the case of peach extract. However, since many enzymes require a specific pH for maximum activity, we were able to preserve the allergenic activity of the fresh peach juice by an alkaline reaction of pH 8.5. Alkalinization did not prevent the ultimate deterioration of the extract, although it did prolong its stability for a short while.

While we may assume that the substance responsible for the deterioration is an enzyme, and also that its activity may be held in check in the intact fruit by an enzymase, we have no definite evidence to prove this

assumption. It is hoped that its exact nature will be more clearly defined by future biochemical investigations; such investigations already have been instrumental in detecting the existence of proved enzymes in such fruits as pineapple and papaya. We have reason to believe from limited and incomplete investigations of other fresh fruits, that a similar situation exists among them. Isolation of the agent responsible for the deterioration in fresh peach juice might act, therefore, as a prototype of other fresh fruits.

The results of these studies, even though admittedly inconclusive, already are of some clinical importance. They explain, for example, the failure to obtain positive skin tests with our present extracts in patients clinically sensitive to fresh fruit. Any positive reactions obtained with the latter are the result of good fortune rather than good planning and usually are minimum in degree. Skin tests with such fruit extracts obviously are not dependable. We have been unable as yet to prepare an extract of fresh fruit which will remain stable for a long period of time. In testing the suspected patient, it is necessary therefore to use either the freshly extracted juice or freshly diluted lyophilized extract. The latter has been found to retain its stability fairly well and can be used in skin testing. However, it has the decided disadvantage that it must be used as soon as possible after being diluted to its original state, since it will not retain its allergenic properties any longer than the ordinary fresh juice. The use of freshly extracted or of lyophilized juices is not always easy in actual practice but is the only exact method we have available until some better way of preserving the stability of the fresh juice is devised. If the fresh fruit is used, it is well to adjust its pH to 8.5 and use a 1:5 dilution of this extract for skin testing. The concentrated, alkalinized juice is irritating and will provoke nonspecific reactions. Our diluted extract remains fairly stable for about three months when kept at low temperatures.

Finally, the results of our experiments are helpful in the application of the method of clinical trial to patients with histories of sensitivity to the fruits and negative skin reactions. Clinical tests should be performed only with the fresh or rapidly frozen fruit since the allergenic properties of the stewed or canned fruits are destroyed by heating. This fact explains, too, why patients clinically sensitive to the fresh fruit usually can take the stewed or canned fruit with impunity.

CONCLUSIONS

1. The agent responsible for the deterioration in fruit extracts apparently is linked closely with the active allergenic molecule. It cannot be separated from the molecule by precipitating the protein nitrogen fraction with phosphotungstic acid.

2. Attempted oxidation and the addition of sodium cyanide failed to alter the allergenic activity of the fresh fruit.

3. The rate of deterioration was not influenced by change of the pH to 4.5, but an alkaline reaction (pH 8.5) seemed to prolong its activity for a limited time only.

4. The nature of the substance responsible for the deterioration must await further biochemical assays for its identification. Its behavior in these experiments and the existence of similar substances in other fruits (papaya and pineapple) suggest that the deterioration may be enzymatic in nature.

5. For the present, skin tests done to detect fresh fruit sensitivity, at least with peach extract, should be performed with a 1:5 dilution of the alkalinized (pH 8.5) fresh juice or its lyophilized extract.

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THE PROBLEM OF ALLERGY AT AN ARMY AIR FORCES HOSPITAL

I. Respiratory Allergy (Hay Fever, Vasomotor Rhinitis, and Bronchial Asthma)

Major Stanley F. Hampton, Medical Corps, and
Captain Harold Rand, Medical Corps

INTRODUCTION

THE nature of allergic diseases requires a plan of diagnostic approach in *military allergy* to be so organized that the allergist may prognosticate, as exactly as possible, the extent to which any given soldier may carry out full duties without hindrance from symptoms. This applies to the greatest degree in the field of aviation medicine since regulations governing the qualifications of aviation cadets and rated flying personnel require that they suffer from no abnormality that would interfere with flying.

The only adequate available statistics of allergic diseases during World War I are those on bronchial asthma. Based on the medical records of the United States Army[1] from April, 1917, to Dec. 31, 1919, these letters reveal that 7,797 enlisted men and 221 officers of the American troops were admitted to army hospitals with bronchial asthma. This is a ratio of 1.91:1,000. There was a total of thirty-six deaths, including two officers, with diagnoses of asthma, a ratio of 0.01:1,000. Two thousand nine hundred two Certificates of Disability for Discharge were issued, including seventeen to officers, because of asthma. Vaughan,[2] reviewing the problems of allergy in wartime, stated that individuals with bronchial asthma were rejected by draft boards only when the disease was associated with emphysema or bronchitis, and that rejections were 2.45:1,000.

In one of the surveys of World War II, Hyde[3] and Hyde and Kingsley,[4] in a report of 60,000 consecutive examinations of selectees at the Boston Induction Center, revealed that 1 of 120 examinees and 2.3 per cent of all rejected cases were so rejected because of allergic diseases.

Allergic surveys in military installations by Crandall,[5] Blank,[6] and French and Halpin[7] indicate the importance of control of allergic conditions. French and Halpin[7] have shown that a unified, controlled allergy service composed of fifty-nine army hospitals under a central jurisdiction and supplied by a central allergy laboratory offers the best system for the diagnosis, treatment, and disposition of cases of hay fever, asthma, and allied conditions.

This presentation is a report of the activities and the plan of diagnosis and disposition of AAF personnel suffering from, suspected of

having, or having had, one or more of the clinical syndromes of respiratory allergy (hay fever, vasomotor rhinitis, and bronchial asthma) as encountered by the Allergy Section and Clinic at the AAF Regional Hospital of San Antonio Aviation Cadet Center, Texas, from Aug. 1, 1942, to Aug. 1, 1943.

CLASSIFICATION OF PATIENTS

Eight thousand four hundred nine clinic visits were made by AAF personnel to the Allergy Clinic for diagnosis and treatment, or disposition, during this fiscal year. There were 1,541 new cases, an average of 5.45 clinic visits per patient.

The cases were classified according to status, as candidates for aviation training, aviation cadets undergoing preflight training at this post, enlisted men, officers, and military dependents (Table I).

Four hundred forty-nine cases were examined in an attempt to determine the presence or absence of allergic disorders and if present, whether or not they were of sufficient degree to warrant disqualification for aviation training.

Four hundred ninety-eight patients were admitted to the hospital wards for emergency treatment or to facilitate the establishment of diagnoses for disposition purposes.

TABLE I

CLASSIFICATION OF PATIENTS EXAMINED BY ALLERGY SECTION, AAF REGIONAL HOSPITAL, SAN ANTONIO AVIATION CADET CENTER, SAN ANTONIO, TEXAS, AUG. 1, 1942 TO AUG. 1, 1943

STATUS OF PATIENTS	NUMBER OF PATIENTS
Candidates for aviation training (Enlisted trainees)	449
Aviation cadets	395
Enlisted men	443
Officers	145
Civilian dependents	109
Total number of new cases	1,541
Total number of clinic visits	8,409
Average number of clinic visits per patient	5.45
New hospital ward cases	498

PLAN OF DIAGNOSIS

All patients were studied from the following diagnostic viewpoints:

1. History: History-taking has been considered the most important factor in arriving at the proper diagnosis, prognosis, treatment, and establishment of the "line of duty" status. This was particularly true of patients with bronchial asthma who were candidates for Certificates of Disability for Discharge, and of patients with suggestive history of asthma among candidates for aviation training (see *Aviation Medicine and Allergy*).

The following phases of the history have been considered important in diagnosis:

a. Personal past history of definite allergic disease (eczema, urticaria, hay fever, asthma, etc.).
b. Personal past history of repeated respiratory infections.
c. Family history of allergy.
d. Present history in regard to onset of symptoms; seasonal variation; variation during twenty-four-hour periods; relation of symptoms to diet, drug intake, climatic conditions, fatigue, physical exertion, emotional strain, acute respiratory infections, and changes in environment; and results of previous examination and treatment.
e. A review of authenticated communications from physicians concerning any given case.
f. A review of the personal past and present history after routine skin testing.
g. History of known injections of foreign serum (antitetanic serum, antimeningococcic serum, etc.).

2. Physical Examination: The typical, pale, boggy, glistening appearance of the nasal mucosa has been sufficient to make a tentative diagnosis of allergic rhinitis (hay fever or vasomotor rhinitis), whereas, the borderline cases were usually tabled for further study.

A definite diagnosis of bronchial asthma usually has been made only upon eliciting expiratory sibilant and sonorous sounds on auscultation of the chest, regardless of the results of the skin tests and laboratory examinations. The relative or complete relief of the physical signs following the administration of epinephrine hypodermically has been a contributory factor in the diagnosis of asthma. When, in suspected cases of asthma, routine examination of the chest revealed negative findings, auscultation of the chest during forced expiration has frequently demonstrated sibilant and sonorous sounds in otherwise negative cases of *intrinsic* bronchial asthma. When factors in keeping with a diagnosis of asthma (history, sputum and blood eosinophilia, and significantly positive skin tests) were demonstrated in cases showing no physical signs of asthma, an impression of "allergic constitution" was made and the patient was closely observed in the clinic and hospital ward for physical signs of asthma. Occasionally, it was justified to make a diagnosis of bronchial asthma even without the presence of physical signs (from the data accumulated leading to an impression of "allergic constitution").

3. Cytology: Cytological examinations of nasal secretion were performed on all cases examined for allergic rhinitis, either seasonal or perennial. Two routine smears were made on an ordinary glass slide, one of the smears being prepared by securing the secretion with applicator sticks, the other smear being prepared from the nasal secretion obtained by having the patient "blow his nose" into waxed paper as suggested by Hansel.[8] Additional smears were examined in cases sus-

pected of having nasal allergy when two routine examinations failed to show eosinophiles, although this was rarely necessary.

Three successive daily cytological examinations of the sputum were performed routinely, with additional examinations when warranted, in all cases of suspected asthma.

All nasal secretion and sputum smears were routinely fixed in methyl alcohol for five minutes and stained with freshly prepared Giemsa's stain in a 1:1,320 dilution for twenty minutes.

Three cytological examinations of the blood were performed routinely on all cases of suspected asthma.

4. Skin Tests: A modification of the allergy examination Form 55 E-9 (Medical Department, U. S. Army, 1939) has been adopted at this Hospital. Routine skin tests were performed with eighteen pollen and inhalant extracts* (Series I) and eighteen food extracts (Series II). Additional skin tests were performed as the cases so indicated. The majority of the extracts were standardized on the basis of the total nitrogen or the protein nitrogen content (PNU).[9] The routine testing strength of pollen and inhalant extracts was 100 PNU per c.c., or 1,000 PNU per c.c.

All skin tests except those with bacterial and fungus extracts were performed intracutaneously on the upper arm. Routinely, the entire Series I was tested at one sitting, while Series II was tested at a second sitting. Skin tests were performed by the injection, just beneath the superficial layer of skin, of the smallest volume of extract (0.02 to 0.01 c.c.) that would produce an easily recognized bleb. All bacterial and fungus extracts were tested routinely on the flexor surface of the forearms by using 0.05 c.c.

All cases of hay fever were skin tested with various dilutions of multiples of 10 of pollen extract. These cases were thus classified according to the degree of skin sensitivity depending upon the weakest strength of extract that would give a positive skin reaction which showed pseudopodia. Positive reactions with extract containing 10 PNU per c.c. designated Class A sensitivity, with extract containing 100 PNU per c.c., a Class B sensitivity, etc., as described by Vander Veer and his associates.[10]

5. Bacteriologic Examinations: Bacteriologic culture examinations were carried out routinely on three specimens of sputum in all cases of bronchial asthma for the possibility of autogenous vaccine therapy in cases showing significant bacteria. Cultures were frequently performed on nasal secretions or sinus washings.

6. Vital Capacity: Vital capacity determinations were performed in cases of asthma.

7. Dietary Regimen: Food diaries were utilized by patients with sporadic symptoms, and trial elimination diets (for periods of seven

*Many of the pollen and inhalant extracts were obtained through the courtesy of the Office of the Surgeon, 4th Service Command, Atlanta, Georgia. The others were prepared at this hospital.

to ten days) were employed in cases of constant daily symptoms. The presence of food sensitivity was concluded only after relief of symptoms on such dietary regimen and induction of symptoms upon ingestion of offending foods.

8. X-Rays: X-ray studies of the sinuses were performed in all cases of nasal allergy other than pollenosis and x-ray studies of the sinuses and chest were obtained in all cases of bronchial asthma.

9. Neuropsychiatric Examination: Neurogenic factors have been searched for and evaluated; in many cases, consultations with the neuropsychiatric department have been obtained.

EVALUATION OF SKIN TESTS

The interpretation of skin tests performed with extracts of pollens, inhalants, and foods was made approximately fifteen minutes after testing. The tests with bacterial and fungus extracts were interpreted at twenty-four- and forty-eight-hour intervals.

Positive skin reactions with food extracts were present in approx- the offending allergens but rather as denoting one of four things: (1) present clinical sensitivities, (2) past clinical sensitivities, (3) potential clinical sensitivities, or (4) an "allergic constitution."

Postive skin reactions with food extracts were present in approximately 8 per cent of the total number of patients but were not considered to apply clinically until proved by trial with dietary regimen.

DIAGNOSES

Table II summarizes the diagnoses of the various allergic diseases encountered during the fiscal year. There were 921 cases of respiratory allergy (three-fourths of all allergic diagnoses), 327 cases of other allergic diseases and 303 additional cases (bronchitis, without asthma; sinusitis; headaches; gastroenteritis; etc.) originally thought to be allergic in nature but proved otherwise after thorough study. Pollinosis (hay fever) accounted for approximately one-third of the 921 cases of respiratory allergy.

Hay Fever.—The classification of the different types of 448 cases of hay fever according to etiological factors (pollens) is presented in Table III. There was no difficulty in classifying such cases when they were due to sensitivity to tree, ragweed, grass, or mountain cedar pollens, or to combinations of these pollens. The category, "fall pollens other than ragweed," was assumed in patients with histories of hay fever while residing in sections of the country where pollination of such plants as Russian thistle, chenopod, amaranth, and sage brush occurred when skin tests with extracts of these pollens were of greater intensity than those of ragweed.

All cases of summer hay fever reacting to extracts of plantain pollen also reacted to extracts of grass pollen, and proof of clinical sensitivity to plantain pollen was not attempted. Likewise, although positive skin

TABLE II

ALLERGIC DIAGNOSES

DIAGNOSES*	NUMBER OF CASES
Hay fever (pollinosis)	448
Rhinitis, vasomotor	187
Asthma, bronchial	286
Urticaria, acute and chronic	117
Angioneurotic edema (without urticaria)	16
Dermatitis, atopic (eczema)	24
Epidermophytid (fungus allergy)	44
Dermatitis, contact (dermatitis venenata)	35
Migraine	26
Conjunctivitis, allergic (including vernal catarrh)	13
Serum allergy	75
Serum sickness	7
Gastrointestinal allergy	3
Miscellaneous (cases of dermatographia, Arthus' phenomenon, tetanus toxoid sensitivity, grain inhalation sensitivity, etc.)	49
No allergic disease (patients suspected of having allergic disease, proved not to be the case after diagnostic study)	303
Total	1,633

*Ninety-two cases had multiple diagnoses (actual number of cases 1,541).

TABLE III

CLASSIFICATION OF CASES OF HAY FEVER ACCORDING TO ETIOLOGY (OFFENDING POLLENS)

TYPE OF HAY FEVER (ETIOLOGY)	NUMBER OF CASES
Tree only (oak) (spring pollination)	5
Grass only (summer pollination)	86
Ragweed only (fall pollination)	167
Mountain cedar tree only (winter pollination)	13
Fall pollens* only, other than ragweed	21
Combined grass and ragweed	68
Combined ragweed and other fall pollens*	12
Combined tree, grass, and ragweed	6
Combined grass and fall pollens* other than ragweed	8
Combined ragweed and mountain cedar	12
Combined grass, ragweed and fall pollens* other than ragweed	8
Combined grass and mountain cedar	1
History of† ragweed hay fever	21
History of† grass hay fever	15
History of† combined grass and ragweed hay fever	3
History of† fall hay fever (other than ragweed)	2
Total	448

*Fall pollens, other than ragweed, such as Russian thistle, lamb's-quarters, carelessweed, and prairie sage.

†"History of" refers to no symptoms of hay fever within two years.

tests with extracts of common air-borne molds were frequently obtained, statistical analysis of mold sensitivity was not attempted in this review.

Spring tree, grass, ragweed, and winter mountain cedar tree pollens played a part in the production of hay fever either individually or in combinations in 583 instances (Table IV).

Rhinitis, Vasomotor.—The etiological factors in the 187 cases of perennial allergic rhinitis were difficult to determine, since the presence or absence of positive skin reactions did not necessarily indicate them. Final impressions as to "causes" were deferred until clinical response to

treatment was observed. Five general classes of vasomotor rhinitis were made, as shown in Table V. The etiology in the majority of cases was considered to be inhalants, and house dust reacted the most frequently by skin test.

The category of "intrinsic allergy" (Table V) represents patients associated with suppurative sinus disease, chronic infection of tonsil and adenoids, dental infections, or subnormal thyroid activity, in whom skin tests were negative, or, when positive, were shown clinically to be of no significance. These patients showed clinical improvement (by history, physical findings and nasal cytology) when the infection was treated and vaccine therapy was carried out, or nonspecific therapy such as thyroid extract, vitamins, or histamine injections was instituted.

TABLE IV

ANALYSIS OF ETIOLOGY OF ALL CASES OF HAY FEVER INCLUDING THOSE OF SINGLE AND OF MULTIPLE OFFENDING POLLENS

POLLENS	NUMBER OF CASES
Tree pollens (spring)	10
Grass pollens	206
Ragweed pollens	302
Mountain cedar tree pollens (winter)	17
Fall pollens other than ragweed	48
Total	583

TABLE V

CLASSIFICATION OF CASES OF VASOMOTOR RHINITIS

TYPE	NUMBER OF CASES
Inhalant allergy	70
"Intrinsic allergy"	30
Food allergy	17
Combined inhalant and/or food and/or bacterial allergy	20
Etiology undetermined	50
Total	187

Bronchial Asthma.—Two hundred eighty-six cases of bronchial asthma were examined during the year. Table VI is a summary of these cases according to etiological factors. Ninety cases were associated with chronic respiratory infection, 50 with acute respiratory infections, and 51 of the 75 cases designated as combined etiology had chronic respiratory infection. Altogether, 191 of the 286 cases of bronchial asthma were associated with acute or chronic respiratory disease. Cases of pneumonitis, acute and chronic bronchitis, tonsillitis, and sinusitis have offered the poorest prognosis and, thereby, present the greatest problem to the military allergist.

It is interesting to note that no cases of asthma were considered to be due to food sensitivity alone. Thirteen of the 75 cases listed under combined etiology were proved to be food sensitive by the disappearance of symptoms when certain foods were eliminated, and induction of symptoms upon subsequent ingestion. Whereas, only 19 cases of asthma were

TABLE VI

ANALYSIS OF ETIOLOGY OF ALL CASES OF BRONCHIAL ASTHMA

TYPE OF ETIOLOGY	NUMBER OF CASES
Pollen sensitivity alone	26
Inhalant sensitivity alone	19
Chronic respiratory infection alone	90
Acute respiratory infection alone	50
Food sensitivity alone	0
Combined acute and chronic respiratory infection, inhalant and/or pollen and/or food sensitivities*	51
Pollen, inhalant and/or food sensitivities	24
History of asthma†	26
Total	286

*See text.

†"History of" refers to no symptoms of asthma within three years.

attributed to inhalant sensitivities alone, 75 additional cases were based on inhalant agents in combination with those of pollen, food, and infection (Table VI).

DIAGNOSIS OF RESPIRATORY INFECTION

Acute Respiratory Infection.—Fifty patients with asthma were considered to have acute respiratory infection. Ten of these had primary atypical pneumonia as proved by roentgenologic examination. The remaining forty were cases of acute upper respiratory infection manifested by fever, and acute inflammation of the nasopharynx, pharynx, tonsils, or paranasal sinuses (suppurative). They had leucocytosis and, occasionally, an increase in the sedimentation rate.

Chronic Respiratory Infection.—One hundred forty-one patients with asthma were considered to have a chronic respiratory infection with or without demonstrable chronic suppurative sinusitis. Such patients had one or more of the following: daily constant cough of years' duration, with yellowish, tenacious sputum; dyspnea and wheezing; an onset usually with an acute upper respiratory infection, whooping cough, measles, influenza, "grippe," acute bronchitis or pneumonia; or, definite exacerbation of symptoms during damp or rainy weather and during acute "head colds."

Physical signs of asthma, in these cases, were usually present day and night even though environmental factors and diet were controlled. The sputum in the majority of cases revealed hemolytic bacteria on repeated cultures. There were usually low-grade leucocytosis, frequently a blood eosinophilia of 5 per cent or more, and occasionally an increase in sedimentation rate. Skin tests with common inhalant and food allergens were negative in ninety and positive in fifty-one cases of this group.

CONSTITUTIONAL ALLERGIC REACTIONS

The incidence of constitutional allergic reactions as a result of skin testing has been relatively low. During the first six months, ten constitutional reactions of the immediate type followed skin testing with

eighteen common pollens and inhalants in strengths of 1,000 PNU per c.c. During the second six-month period, when the strength of the extracts used was reduced to 100 PNU per c.c., only two such reactions occurred. No constitutional reactions followed skin testing with the eighteen common food extracts.

"ALLERGIC CONSTITUTION"

The term "allergic constitution" has been adopted at this station to designate individuals (who do not have dermatographia) who react with significantly positive skin reactions to extracts known not to be irritating, but who do not present physical signs of allergic disease. A history suggestive of allergic manifestations, a past personal and family allergic history, and a demonstrable eosinophilia in secretions or blood have been considered confirmatory evidence of an allergic constitution. When any case has been so labeled, the development of physical and laboratory signs characteristic of allergy was closely observed.

The interpretation of an "allergic constitution" has been of significance in aviation medicine.

CERTIFICATE OF DISABILITY FOR DISCHARGE

The disposition board of [illegible] Hospital recommended 1,191 Certificates of Disability for Discharge during this fiscal year, of which 106 were granted to men with allergic diseases. Of these, 86 were cases of bronchial asthma (Table VII). The majority of these 86 cases suffered from asthma of the intrinsic type associated with acute recurring or chronic respiratory infection. Six patients had pulmonary emphysema. It follows, therefore, that 8.9 per cent of all cases discharged under Section 2, Army Regulation 615-360 (Nov. 26, 1942) had allergic disorders and that 7.48 per cent of all discharged had bronchial asthma. The one case of hay fever receiving a Certificate of Disability for Discharge listed in Table VII received such disposition primarily because of psychoneurosis rather than hay fever.

Only two cases of vasomotor rhinitis were severe enough to warrant discharge from the Army.

ALLERGY AND AVIATION MEDICINE

The physical requirements for aviation training recorded in *Army Regulations* take into account various allergic disorders.

Hay Fever.—AR 40-110, established in 1940, stated that hay fever, or any history of hay fever, was disqualifying for aviation training. Subsequently this regulation was changed to disqualify only individuals who had had hay fever within two years prior to examination regardless of the past hay fever history. The present Army Regulation states that *"hay fever is disqualifying unless the examiner is satisfied it is mild in degree"* (AR 40-110, Dec. 3, 1942).

TABLE VII

SUMMARY OF 106 CASES OF ALLERGY RECEIVING CERTIFICATES OF DISABILITY FOR DISCHARGE*

DIAGNOSES	NUMBER OF CASES EXAMINED		NUMBER OF CERTIFICATES OF DISABILITY FOR DISCHARGE	
Asthma, bronchial, intrinsic	134		50	
Asthma, bronchial, intrinsic with pulmonary emphysema	6		6	
Asthma, bronchial, extrinsic	69		7	
Asthma, bronchial, combined intrinsic and extrinsic	51		23	
Asthma, bronchial, history of	26		0	
Asthma, bronchial Total		286		86
Hay fever		448		1
Rhinitis, vasomotor		187		2
Urticaria		117		7
Angioneurotic edema (without urticaria)		16		2
Migraine		26		4
Eczema (allergic or atopic dermatitis)		24		2
Dermatitis, contact		35		1
Purpura (Schönlein's)		1		1
Other allergic diseases		190		0
No allergic disease		303		0
Total		1,633†		106

*Total number of Certificates of Disability for Discharge issued for all diagnoses during same period was 1,191.

†Ninety-two cases had multiple diagnoses (actual number of cases 1,541).

The diagnosis of hay fever was made for disposition by the history and reactivity to skin tests with pollen extracts as previously described. When the patient was examined during the pollinating season the diagnosis was, of course, easily made by physical signs and by positive skin reactions to the appropriate pollen extracts.

Since December, 1942, when the present regulation governing the *degree* was established, the problem has been more complicated, except in cases examined during the pollinating seasons. The following plan has been used to arrive at an interpretation of degree of hay fever and thereby the prognosis in relation to flying:

1. As accurate a history as was possible was obtained. The association of bronchial asthma with hay fever was considered indicative of *severe* hay fever. The history of associated eye symptoms (redness, itching, and lacrimation) was considered indicative of *moderate* or severe hay fever. The history of nasal symptoms alone was considered as suggestive of *mild* or moderate hay fever. The history, however, varied with the intelligence, the personality, the ambition, and the desirability for flying of the individual. There is no doubt that a man who strongly wishes training in aviation may have a "convenient memory" and underrate the degree of his symptoms.

2. The unreliability of histories in many cases necessitated testing all candidates for aviation training with common inhalants and pollens. In addition, titrations of skin tests, with the pertinent pollen extracts, in dilutions of multiples of 10, were carried out in order to determine the degree of skin sensitivity.

It did not necessarily follow that individuals requiring strong pollen extract to produce a marked reaction had clinically mild hay fever. This type of skin testing, however, together with the information that could be obtained from the history, physical examination, and nasal cytology, was usually sufficient to arrive at the degree of clinical sensitivity.

Rhinitis, Vasomotor.—Candidates for aviation training with vasomotor rhinitis were considered from four main viewpoints: (1) history of duration and degree of symptoms, (2) physical nasal signs, (3) skin tests, and (4) nasal cytology.

The physical signs and cytology were the most important in determining degree. The extent of edema or hyperplasia of the mucosa of the inferior and middle turbinates was graded as mild, moderate, or severe. The presence of over 10 per cent of eosinophiles in the nasal secretion indicated definite allergic activity of the mucosa and was frequently a contributing factor in "borderline" cases. The presence of significant positive skin tests was further evidence of the allergic constitution so that individuals showing only mild nasal signs in the presence of an increased nasal eosinophilia and markedly positive skin reactions were disqualified for aviation training even though the history suggested "mild" symptoms.

Bronchial Asthma.—The original Army Regulations for flying disqualified the candidate who had had bronchial asthma at any time during his life (AR 40-110, December, 1940).

Subsequently, examinations and disposition have been conducted in accordance with the newer and present Army Regulation as follows:

"*History of the following will disqualify original applicants for aviation training and flying personnel on subsequent examinations for flying: asthma of any degree—history of asthma other than in childhood with trustworthy history of freedom of manifestations during the preceding ten years*" (AR 40-110, Paragraph 20, A, [9], Dec. 3, 1942).

When a subject was examined during an acute attack or exacerbation of bronchial asthma the disposition was easily concluded.

The problem of determining the presence or absence of *true* bronchial asthma in the past history of an examinee has been, at times, rather difficult. The history may have been strongly suggestive of asthma, although, in these cases of young individuals (18 to 27 years of age) the episodes of occasional respiratory symptoms in the past may well have been nonallergic (bronchitis, "croup," etc.). A positive family history in such cases was of some significance. Probably the most significant factor, however, was the reaction to skin tests with common allergens. The presence of significantly positive skin reactions, regardless of the allergen, was considered evidence in favor of an allergic constitution and thus evidence that the "asthmatic attacks" in the past history were true bronchial asthma.

Pressure Chamber Studies.—Whereas a controlled series of investigations of patients with nasal allergy has not been conducted, it is the

general opinion that individuals suffering from allergic rhinitis were not affected adversely by changes of atmospheric pressure (in the pressure chamber of this Post) any more than the normal person. Certainly, the symptoms of nasal obstruction, nasal secretion, and sneezing were not increased by relatively rapid changes in atmospheric pressure. The symptoms of aerosinusitis, including pain, that are so common following changes in atmospheric pressure (especially in cases of upper respiratory infection) were generally not observed in cases of allergic rhinitis of moderate or even severe degree.

Incidence of Disqualification for Aviation Training.—Two hundred eighty-three candidates for aviation training were disqualified at the time of the "64" examination for flying (between Aug. 1, 1942, and Aug. 1, 1943) because of allergic disorders. Since 449 cases were examined by the Allergy Section during the same period of time, it follows that 63 per cent of the cases suspected of allergy were disqualified for aviation cadet training. Table VIII shows the various diagnoses of those disqualified because of allergy.

For obvious reasons, the actual number of candidates for aviation training examined during this year should not be released. It will suffice to report that approximately 3.7 per cent of those disqualified were cases of allergy.

TABLE VIII

SUMMARY OF THE DIAGNOSES OF 283 INDIVIDUALS DISQUALIFIED FOR AVIATION TRAINING ("64" EXAMINATION)

ALLERGIC DIAGNOSIS	NUMBER OF CASES
Hay fever	135
Rhinitis, vasomotor	39
Asthma, bronchial	94
Urticaria, chronic	5
Angioneurotic edema	1
Migraine	25
Eczema ("atopic" dermatitis)	16
Purpura (Schönlein's)	1
Allergic constitution	1
Total	317*

*Thirty cases had two allergic diagnoses. Two cases had three allergic diagnoses.

PLAN OF TREATMENT

The plan of treatment of respiratory allergic diseases occurring at an AAF Regional hospital will be reported in a separate article because of the length of this presentation.

DISCUSSION

The problem of allergy in the United States AAF is no small one, as evidenced by the fact that 1,541 cases were examined for clinical allergy at this hospital in one year.

The diagnosis, treatment, and disposition of cases of hay fever and vasomotor rhinitis have not been a problem here. Daily pollen counts

have aided in analyzing the occurrence and intensity of symptoms of hay fever.

The greatest problem of allergy at this hospital has been bronchial asthma caused by, or associated with, respiratory infection. Asthma associated with *acute* respiratory infection (acute upper respiratory infection, acute bronchitis, and pneumonia) has been somewhat self-limited. The asthmatic symptoms and signs usually subsided with the termination of the acute infection, only to recur in some instances with subsequent attacks of respiratory infection. An interesting observation is that asthma occurred in ten cases of primary, atypical pneumonia in individuals who had not had asthma previously. This syndrome will be reported in a separate presentation.

The prognosis of asthma associated with *chronic* bronchitis is poor, as pointed out by Alexander.[11] Some cases associated with chronic tonsillitis or sinus infection have responded favorably by eradication of the focus and by vaccine therapy. Those cases associated with chronic bronchitis, however, frequently did not improve with treatment.

Seventy-eight of the 86 patients who received Certificates of Disability for Discharge because of allergic disorders had asthma associated with chronic respiratory infections. Those with asthma of this type had been unable to carry out full field duty, and, since the prognosis is uncertain, even with long courses of treatment, it was considered the better policy to return these individuals to civilian life.

Each of the seventy-eight patients gave a history of definite asthma, of repeated attacks of "bronchitis," or of chronic cough existing prior to enlistment. The family history of allergy was positive in a good number of the cases. These individuals no doubt were free from signs of asthma at the time of induction. Many of them reacted positively to skin tests, even though the allergens may have played no role in etiology. If time had permitted accurate history taking, and facilities had been present for skin testing during the induction examination, the diagnosis of bronchial asthma could have been made at that time, thus permitting rejection of these cases under MR 1-9 (Oct. 15, 1942).

The most interesting observation of this study was that the group in which a high incidence of respiratory infection was associated with bronchial asthma was made up mostly of young men. Two of the 286 cases were over 40 years of age, 5 were between the ages of 30 to 40 years, and the remainder were between the ages of 18 and 27 years (age limits of aviation cadets). This type of asthma has been commonly observed in individuals over 40 years of age in civil practice as pointed out by Cooke,[12, 13] Alexander,[11] and Rackemann,[15, 16] and Rackemann and Mallory.[14] One hundred forty of the 286 cases of asthma were associated with respiratory infection and an additional 51 cases had respiratory infection associated with extrinsic etiological factors (pollens, inhalants, and foods). Thus, 191 (67 per cent) of the 286 cases of asthma were associated with respiratory infections.

SUMMARY

1. A report of the activity of the Allergy Section and Clinic, AAF Regional Hospital, San Antonio Aviation Cadet Center, San Antonio, Texas, from Aug. 1, 1942, to Aug. 1, 1943, has been presented.

2. Eight thousand four hundred nine clinic visits were made by Air Forces personnel to the Allergy Clinic of this Hospital.

3. One thousand five hundred forty-one new patients were examined by the Allergy Section of this hospital.

4. Nine hundred twenty-one of the 1,238 cases of allergic diseases were respiratory allergy (hay fever, vasomotor rhinitis, and bronchial asthma).

5. One hundred six or 8.9 per cent of the 1,191 men receiving the Certificate of Disability for Discharge under Section 2, AR 615-360 (Nov. 26, 1942), had allergic diseases. Eighty-six or 7.48 per cent had bronchial asthma.

6. Three and seven-tenths per cent of candidates for aviation training who were disqualified because of failure to meet the physical requirements (AR 40-110, Dec. 3, 1942) had allergic disorders.

7. The factors used in determination of fitness for aviation training of individuals with or suspected of having respiratory allergic disease are discussed.

8. The greatest problem of allergy has been *intrinsic* bronchial asthma associated with chronic respiratory infection. The high incidence of this syndrome in the young Air Forces age group is discussed.

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Editorial

Periarteritis Nodosa and Rheumatic Fever Manifestations

ALMOST two decades ago, Gruber[1] suggested that periarteritis nodosa may be an allergic disease. Ten years later, Kline and Young[2] demonstrated three cases in which allergy was a factor. Cohen, Kline, and Young[3] showed that a clinical diagnosis of periarteritis nodosa could be made on biopsy, and that this disease is a severe allergic reaction in the blood vessels. Berger and Weitz[4] corroborated previous findings in reporting a patient in whom asthma and periarteritis nodosa were associated. The association of asthma and periarteritis nodosa in eight patients observed by Rackemann and Greene[5] is particularly interesting.

It is, however, the experimental and clinical observations of Rich and Gregory in the last two years that have focused our attention on this problem. The first contribution of Rich[6] called attention to the finding of typical lesions of periarteritis nodosa in seven patients who had serum sickness as a result of serum administration. In six of these cases, the lesions were found in the viscera, at autopsy; in the seventh case, they were found in a muscle biopsy. Four of these patients had had sulfonamides in addition to the serum. In that paper, Rich was of the opinion that this type of vascular lesion is a manifestation of the anaphylactic type of hypersensitiveness and suggested further that, in cases of periarteritis nodosa coming under observation, a search be made for the causative antigen. Subsequently, Rich[7] reported fresh and generalized lesions of typical periarteritis nodosa found at autopsy in a Negro who had fever and conjunctivitis from continued sulfathiazole administration during the pre- and postoperative course of a scrotal malignancy. Of great interest are the facts that preoperative examination of some of the same tissues prior to the administration of sulfathiazole showed no vascular lesions, that no serum was administered in this case, and that the symptoms and other pathologic findings resemble those previously described by others as due to toxic reactions from sulfonamides. Rich concludes the paper with the warning that "these observations indicate that the continued administration of a sulfonamide or of foreign serum after symptoms of hypersensitivity have appeared, or the injection of a single large amount of foreign serum, carries the danger of producing vascular damage of the periarteritis nodosa type."

Following these significant clinical observations, Rich and Gregory[8] showed further that typical periarteritis nodosa was produced in rabbits after serum sickness. They also found that acute diffuse glomerulo-

nephritis occurred in a number of the rabbits that developed a hypersensitive reaction to the foreign serum and suggest that: "This supports the view that some cases of glomerulo-nephritis in man may be due to hypersensitivity."

A large percentage of the rabbits with experimental serum sickness developed cardiac lesions that resembled those of rheumatic carditis.[9] The changes noted were focal alterations in the collagen of the connective tissue; focal edema; inflammatory pericardial, mural, and valvular infiltrations; and nodular focal cell accumulations in the endocardium, valves, and adjacent to the arteries in the connective tissue septa of the myocardium. The authors cite some pertinent circumstances that are consistent with the view that the lesions of rheumatic fever may be the result of the anaphylactic type of hypersensitiveness: (1) Focal injury to connective tissue is common in both conditions. (2) Rheumatic arteritis, resembling pariarteritis nodosa, occurs in rheumatic fever. Similar lesions have been described in the animals. (3) Skin manifestations of serum sickness type (urticaria, erythema) occur fairly frequently in the course of rheumatic fever. (4) Purpura is a recognized manifestation of rheumatic fever and of serum sickness and allergy. (5) Tissue eosinophilia occurs frequently in rheumatic hearts. (6) Acute rheumatic fever has many features in common with the anaphylactic reaction of serum sickness: fever, arthritis, anaphylactic, cutaneous lesions and arterial lesions. Reports in the literature also indicate that human serum sickness may cause cardiac changes. (7) Synovial exudate from rheumatic fever joints and arthritis of serum sickness appear to be identical.

Rich and Gregory[10] have recently presented additional evidence for the view that the lesions of acute rheumatic fever may be anaphylactic in origin. They found that the lesions of rheumatic pneumonitis and the pneumonitis produced by sulfonamide hypersensitivity were basically identical, consisting of the typical primary capillary damage characteristic of focal anaphylactic reactions.

The above observations should teach us much in the way of facts, speculation and stimulation to drive us along newer and fresher experimental paths. Great light has been shed on the etiology of periarteritis nodosa and suggestive evidence has been presented to indicate that at least some of the manifestations of rheumatic fever are also on the basis of similar hypersensitiveness. The potential dangers of serum sickness and reactions from drugs, particularly sulfonamides, should enter our consciousness when we are tempted to give sera or sulfa drugs indiscriminately. The work of Rich and Gregory, however, deserves special commendation because of its contribution to the understanding of the phenomenon of hypersensitiveness and because of the function it will serve in stimulating further investigation along basic lines in this field.

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—*S. M. F.*

Negative Reports

WHEN the experimenter, after months of diligent work and fond hopes for a successful outcome, has finally wound up with an array of negative findings that shatter his theories, the chances are good that he will try to forget his disappointments and say nothing, at least in print. It frequently also happens that many workers will obtain results entirely different from those reported by the original experimenter or clinician, and yet very few of these findings are made available to those who are to use the facts. It is a common human trait to report the positive data and to remain silent about the negative. It appears to amount to a subconscious feeling that to say something good or confirmatory about a therapeutic method, a diagnostic procedure, or an etiologic factor is not only laudatory to the principle involved, but also to the author; to say that it has no value or that the author, after hoping to find something, ended up in nothing, has the sting of self-criticism. Every person who has made positive contributions to scientific progress has also participated in researches which have ended in disappointments. They are the natural by-products of all investigations. Furthermore, they constitute the blind alleys which are so valuable to the experimenter because each one bears a sign: "Do not proceed further; turn back!" Silence about negative findings encourages repeated and unnecessary pieces of work on the part of a number of others. Silence about negative results in fields in which previous positive claims have been made serves to continue the stamp of approval which is often undeserved. Many of us have been guilty of this sin of

omission. Many of us could have saved ultimate embarrassment to the general medical profession and the misguiding of the public if we had been more ready to publish our usual negative findings with such therapeutic procedures as calcium, histamine, vitamins, vaccines, potassium chloride, nasal filters, and other modalities. For example, the writer's failure to publish his negative therapeutic results from the administration of vitamin E in a variety of atopic conditions, undoubtedly led to the continuance of considerable use of vitamin E in allergy and necessitated at least one other piece of research in that direction (Glaser and Dam) with its concomitant waste of energy and time. The same thought, of course, applies to diagnostic procedures and negative findings in experimental problems. Let us not shun the duty of reporting negative findings; they should be brief, but should be published.

—S. M. F.

Symptoms of Hay Fever and Blocking Antibody

IN THIS issue, two contributions appear which deal with the correlation between the titer of thermostable (blocking) antibody to ragweed pollen antigen, and clinical improvement. Loveless finds such a correlation in a large majority of cases. Gelfand and Frank, on the other hand, maintain that clinical results apparently do not depend upon high blocking antibody titers, and found that the percentage of good results was identical in those who had low and in those who had high titers.

Here, then, is controversy over a point of much clinical importance. It is entered into by experienced observers whose factual results should not be questioned. It is apparent, however, that the inherent difficulties of the problem involved are substantial. To begin with, the technical performance of measuring accurately the titers of blocking antibody by means of passive transfer is open to wide variation. Secondly, estimation of clinical improvement, which is one of the two variables in the problem, is based on no common standard. This fact, in turn, emphasizes the comparatively small series from which inferences have been drawn, although the great amount of work involved to secure these results is recognized.

It would seem, therefore, that the question should remain open, pending confirmation. The use of the quantitative precipitin method recently described for measurement of thermostable antibody should determine this value with considerable accuracy. Larger series would tend to diminish factors of variability in the estimation of clinical improvement. In time, this important problem, it is believed, will be resolved into the correct answer.

H. L. A.

Annual Meeting

THE AMERICAN ACADEMY OF ALLERGY

THE first annual meeting of the Academy will be held at the Waldorf-Astoria Hotel in New York City next December 11 and 12. Due to the significance of this occasion, a large attendance is anticipated. Those who expect to be present are urged to apply for hotel reservations immediately. Rooms are still available, but these will be taken up long before the meeting. The program committee has been fortunate, not only in receiving acceptances from several distinguished guest speakers, but in assembling significant contributions from the membership of the Academy.

Program

MONDAY, DEC. 11, 1944

Session I

(9:00 A.M. Promptly)

Each member must complete his presentation within the time limit specified. Members only are permitted to enter the general discussion, to be limited to ten minutes for each presentation, two minutes of which will be allotted to the chief discusser.

1. Diagnosis and Treatment of Allergic Manifestations of the Cornea.
   J. Warrick Thomas, M.D., and, by invitation, F. B. House, M.D. (twelve minutes).
2. Moisture Characteristics of Pollen.
   Arthur B. Berresford, M.D., and Robert A. Cooke, M.D. (twelve minutes).
3. Allergy in Relationship to Internal Medicine.
   By invitation, David Barr, M.D., President-elect of The American College of Physicians.
4. A Brief Review of the Clinical Importance of the Rh Factor.
   Philip Levine, M.D. (twelve minutes).
5. Treatment of Urticaria With Synthetic Vitamin K.
   J. Harvey Black, M.D. (twelve minutes).
6. An Active, Stable, Poison Ivy Extract in Normal Saline Solution.
   By invitation, Margaret B. Strauss, B.A., and W. C. Spain, M.D. (twelve minutes).
7. Skin Reactions to Human Dander.
   Frank A. Simon, M.D. (twelve minutes—to be read if time permits).

Session II

(2:30 P.M. Promptly)

8. "Depletion" in Asthma.
   Francis M. Rackemann, M.D. (twelve minutes).
9. Nutritional Aspects of Globulin Metabolism.
   By invitation, Paul R. Cannon, M.D., Chairman, Department of Pathology, University of Chicago.
10. Treatment of Ragweed Pollinosis With Antibody Neutralized Extracts. Preliminary Report.
    Milton B. Cohen, M.D., and Harold J. Friedman, M.D. (twelve minutes).
11. Reactions to Pneumococcus Antiserum. Reversed Passive Anaphylaxis in Guinea Pigs; Primary Toxicity of Antiserum.
    Oscar Swineford, Jr., M.D. (twelve minutes).
12. A Study of the Fungus Contaminants of the Air of San Diego and Vicinity With a Note on the Relative Importance of Fungi and Pollens.
    George F. Harsh, M.D., and, by invitation, Sonia E. Allen, B.A. (twelve minutes).
13. A Clinical and Experimental Evaluation of Niacin (Nicotinic Acid).
    Armand E. Cohen, M.D., and, by invitation, Lloyd D. Mayer, M.D. (twelve minutes—to be read if time permits).

DINNER

ASTOR GALLERY

7:00 P.M.

TUESDAY, DEC. 12, 1944

Session III

(9:00 A.M. Promptly)

14. Presidential Address.
    Robert Chobot, M.D.
15. Business Session.
16. Factors Influencing Capillary Permeability.
    By invitation, Eugene Landis, M.D., The George Higginson Professor of Physiology, Harvard Medical School.
17. The Significance of Histamine in Anaphylaxis.
    By invitation, Carl A. Dragstaedt, M.D., Professor of Pharmacology, Northwestern University Medical School, Chicago.
18. Panel Discussion. Importance of Paranasal Sinusitis in Bronchial Asthma.

LUNCHEON

1:30 P.M. Wedgewood Room

19. The Allergenic Properties of Azochloramid Disinfectants.
Samuel M. Feinberg, M.D., and, by invitation, R. M. Watrous, M.D. (twelve minutes).

20. Diseases of Adaptation.
By invitation, Hans Selye, M.D., Associate Professor of Histology, McGill University.

21. Cutaneous Absorption. III. The Transport of Antigen Through the Body by Electrophoresis.
Abraham Walzer, M.D., and Harry Golan, M.D. (twelve minutes).

22. Measurement of Circulating Ragweed Antigen.
By invitation, Mary Johnson, B.A., and Harry L. Alexander, M.D. (twelve minutes).

23. Studies in Food Allergy: Variations in Allergenic Activity of Food Extracts.
Louis Tuft, M.D., George I. Blumstein, M.D., and, by invitation, L. J. Wenger, M.D. (twelve minutes—to be read if time permits).

News and Notes

Postgraduate Course in Allergy Under the Auspices of the American College of Physicians

THE American College of Physicians has announced an intensive postgraduate course in allergy to be given under the direction of Dr. Robert A. Cooke at the Roosevelt Hospital, New York City, Oct. 16 to 21, inclusive, 1944. The course will include lectures, clinics, and conferences, and, while it will be given at the Roosevelt Hospital, the Officers of Instruction will be drawn from many medical schools and hospitals. All phases of allergy—immunologic, pathologic, and clinical—will be covered, including theoretical and practical aspects with the idea of furnishing the internist, the general practitioner, or the allergist with the latest information. There will be one optional session devoted to the allergen extracts and vaccines, and practical experience in testing.

Through the courtesy of Dr. Cooke and the Committee on Postgraduate Education of the American College of Physicians, approximately twenty places in this course will be reserved for members of the American Academy of Allergy and for a small group of South American physicians, the Inter-American Group, sponsored by the Pan American Sanitary Bureau and the Division of Health and Sanitation at Washington, D. C.

The Executive Offices of the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania (where application should be made, in care of Dr. E. A. Loveland), has agreed to mail copies of the Postgraduate Bulletin in which this course will be outlined, to all members of the American Academy of Allergy about September 5. The fee will be $40.

Officers of instruction will include Drs. Cooke, Horace Baldwin, Aaron Brown, Robert Chobot, Russel Grove, Selian Hebald, Joseph Harkavy, Paul Klemperer, Will Spain, Louis Schwartz, Albert VanderVeer, and Mathew Walzer.

The Committee on Education has recommended that the Academy sponsor similar courses throughout the country. Groups of thirty or more physicians, who need not be connected with the Academy, may apply for such a course through a member or fellow, to act as sponsor. The faculties will be national in character. Further information may be secured from Dr. Robert A. Cooke (60 East 58th Street, New York City), chairman of the Committee on Education.

Awards

Three prizes are offered by the Academy for meritorious work in allergy. The first is the "Marcelle Award" of $500, granted annually

through the generosity of the Marcelle Cosmetic Company. The second is designated the "Abbott Laboratories Allergy Award." This is a $200 prize offered annually by the Abbott Laboratories. The stipulations covering these awards are broad. Each is offered to any individual or group, whether or not associated with the Academy, who, in the opinion of the Merits Committee, has made outstanding contributions in the field of allergy. Such work may be expressed in research, clinical investigation, book form, or in any other way deemed suitable by the committee.

The third award is the Secretary's prize, donated through the generosity of Dr. Will C. Spain. This, a scroll or medal, will be presented annually to a member or fellow of the Academy, who, in the opinion of the Merits Committee, has done most to further the interests of the Academy.

Miscellaneous

A directory is being compiled by the Secretary. This will include not only names and addresses of the membership, but hospital affiliations, teaching appointments, and data designed to make such a directory a useful book of reference. To compile these statistics is a painstaking task. Most of the members and fellows have promptly completed and returned the questionnaire sent to them several weeks ago. The work is now being held up pending receipt of outstanding forms. It is urged that those who have not done so, return this information to Dr. Spain promptly, so that the work can go on. If no data is available of those who fail to cooperate, deletions will necessarily occur.

Many applications for membership to the Academy have been received, in which the forms were incompletely executed and were returned to the sponsors. The Credentials Committee urges that attention be paid to the detailed directions that accompany the application forms.

Erratum

"A Quantitative Method for Measurement of Precipitin Reactions" by Johnson et al., appearing in the March issue of the JOURNAL, volume 15, page 83, should be corrected as follows: page 87, line 5, 1.055 should read 0.1055; line 6, 1.055 should read 0.1055, and 5.26 should read 0.526.

Book Review

Allergy in Practice. Samuel M. Feinberg, M.D., Chicago, 1944, The Yearbook Publishers, Inc., pp. 798, illustrated.

In evaluating yet another book on clinical allergy, the question may be fairly asked, "What is the purpose of this work?" The author answers it in the preface wherein he states that with few exceptions most texts on the subject appearing in the last few years have been either too elementary or too elaborated. The objective in this book was to set forth a practical exposition of the subject, detailed enough to be useful but not encyclopedic. In this, the author succeeded admirably. Clarity of presentation, sequence, and selection of references, are excellent. It is truly a textbook. In controversial discussions, the author offers his own interpretation, and he fairly states those of others. Special features are a rather extensive exposition of mold allergy, with which the author is very familiar, and the collaboration of Durham in the discussion of hay fever.

As a presentation of allergy, particularly in its conventional sense, the book is all that it pretends to be. Adverse criticism would concern its balance. It reassembles and exposes with clarity much of the conventional material. The author does deal briefly with the broader concepts of allergy but much of what is known about them is reaching us through others than allergists. The relationship of periarteritis nodosa to asthma, true allergic aspects of rheumatic fever, mediation of adrenal secretions to these mechanisms, newer conceptions of the interrelationship between histamine and acetylcholine and their reciprocal enzymes, are but a few of the challenging things about which we wish to know more. This reviewer believes that such subjects no longer should be looked upon as postgraduate, but should be given adequate consideration so that our horizons may broaden.